DERMOBIOTICA
MICROBIOTA E PELLE

Modena, 29 novembre 2018

Il microbioma cutaneo nella psoriasi e nella dermatite atopica

Stefania Farina

TERME DI COMANO

ISTITUTO G.B. MATTEI
RICERCA IN IDROLOGIA MEDICA E MEDICINA TERMALE

Terme di Comano

In ambiente termale punto di riferimento nella cura della pelle e in particolare delle malattie infiammatorie croniche della pelle come psoriasi e dermatite atopica

Dimostrazione scientifica di efficacia

- CURE TERMALI PRATICATE FIN DALL'ANTICHITÀ E ANCORA OGGI POCO CONOSCIUTE DA PARTE DEI MEDICI

- **Riserve riguardo la dimostrazione scientifica**

- L'acqua termale agisce attraverso diversi meccanismi: meccanico-plastico, termico, chimico e immunologico

- **JAMA 100 Years Ago** | May 17, 1913| May 15, 2013

JAMA 2013;309(19):1975.

NEW ANALYSES OF HOT SPRING WATERS

Hot springs are found in many parts of the world. Where they are reasonably accessible they are frequently made a part of a "health resort" established to exploit the curative properties of the waters. The heating of the springs is probably accomplished by deep-seated waters which are converted by contact with heated masses in the interior of the earth into vapor. This ascends through fissures toward the surface, where it meets cold springs and heats them.

When it is remarked that "hot water is hot water anywhere," so that this feature of hot springs need not induce patients to travel away from home to obtain the benefits of thermotherapy, the enthusiasts for these health resorts assure us that the waters contain other features than the heat. In many cases chemical analysis has failed to reveal any unusual content of mineral constituents to account for the alleged therapeutic effects. This is true, for example, of the waters at Hot Springs in Arkansas, where the government reports freely admit that the dissolved matter is low in amount. These waters, like those of some other deep springs, are radio-active; and in the absence of more convincing evidence along other lines the therapeutic value of the baths at the Arkansas Hot Springs is attributed to the radioactivity of the waters rather than to any mineral constituent. The use of the waters is, however, combined with so many other features of hydrotherapy, thermotherapy, dietary supervision and hygienic living that it must remain an open question whether in truth the waters *per se* have any specific curative virtues.

It is important to have full information regarding all the factors in connection with such resorts, so that an unbiased estimate of their real merits can be frankly made known. A recent report to the United States Geological Survey brings facts regarding the waters of the Breitenbush Hot Springs.[1] They are situated near Breitenbush Creek on the west slope of the Cascade Mountains in Marion County, Oregon. The valley of the Breitenbush is narrow, and the formations exposed are lavas of the Cascade Range series. More than sixty hot springs, in three general groups, lie along both sides of the stream for almost a third of a mile. A few cold springs, entirely different in character, are within the limits of the groups, but as they are normal for the region they are unimportant. All the hot springs have nearly the same temperature, and the manner of their grouping suggests a common origin. Reputed curative properties have been assigned to the various springs, and a crude "health resort" has been constructed. Many patients take the waters each year, and if the place were more readily accessible it would undoubtedly enjoy a large patronage. The government analyses now published show that the several hot springs are merely separate outflows from a common source. The water is characterized by a content of sodium chlorid of approximately 1.5 parts per thousand, resembling other "salt" waters; but it contains small amounts of silica, calcium, bicarbonates and sulphates. The report suggests that "minimum medicinal doses of both sulphates and carbonates might be obtained by drinking about 4 liters [4 quarts] of the water, but the disagreeable and even nauseating taste of the chlorids would make the drinking of that amount in one day a herculean feat. It is certain that any curative properties attributable to the mineral content are psychologic rather than physiologic." Without prejudice as to other therapeutic possibilities, of which the still problematic radio-active hypothesis may be one, the possession of authentic information regarding all such reputed health-giving agencies is greatly to be desired as an aid to rational critique and just appreciation. To seek light in this domain is not necessarily to deny the testimony of empiric clinical experience.

1. The data are given by W. VanWinkle in Jour. Ind. and Eng. Chem., April, 1913, p. 300.

JAMA. 1913;60(20):1542-1543

Editor's Note: JAMA 100 Years Ago is transcribed verbatim from articles published a century ago, unless otherwise noted.

JAMA 100 Years Ago Section Editor: Jennifer Reiling, Assistant Editor.

Terme di Comano e Ricerca

PROVATI RISULTATI TERAPEUTICI
PUBBLICATI SU RIVISTE INTERNAZIONALI

ATTENZIONE ALLA RICERCA SCIENTIFICA
E CAPACITÀ DI GESTIRE STUDI RIGOROSI

“medicina basata sulle prove di efficacia”

Studi clinici sulla terapia della psoriasi alle Terme di Comano

- Zumiani G, Tasin L, Urbani F, Tinozzi CC, Carabelli A, Cristofolini M. Clinico-statistical study on hydropinic and balneothermal therapy of psoriatic patients using the low mineral-content waters of the Comano springs. *Minerva Med* 1986;77:627-34.

- Zumiani G, Zanoni M, Lo Brutto R, Cristofolini P, Tasin L. Bath-photo-therapy with the thermal water of Comano: treatment of psoriasis. *Acta Derm Venereol* 1989;146:122-4.

- Agostini G, Agostini S, Bauer P, Cristofolini P, Zanoni M. Modificazioni funzionali in corso di balneoterapia alle Terme di Comano. *Clin Term* 1992; 45: 155-68.

- Zumiani G, Zanoni M, Agostini G. Valutazione dell'efficacia dell'acqua della fonte termale di Comano versus acqua di acquedotto nella cura della psoriasi. *G Ital Dermatol Venereol* 2000;135:259–63.

Dermatologic Therapy, Vol. 21, 2008, S31–S38
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DERMATOLOGIC THERAPY
ISSN 1396-0296

Balneotherapy for chronic plaque psoriasis at Comano spa in Trentino, Italy

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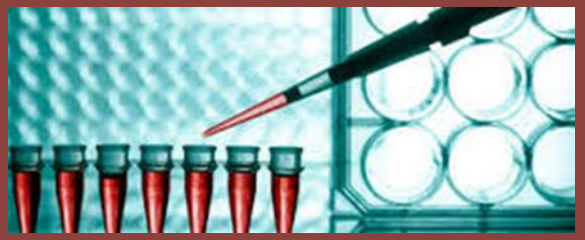
ABSTRACT: Thermal therapy is used worldwide in the treatment of psoriasis but few controlled studies have evaluated its efficacy and safety. We studied the efficacy and safety of balneotherapy compared to photobalneotherapy performed at Comano spa in Trentino, Italy, in chronic plaque psoriasis in a prospective, nonrandomized, open study. Three hundred adult patients with mild to severe chronic plaque psoriasis were assigned to either balneotherapy or photobalneotherapy with daily narrow-band ultraviolet B for a mean period of 1 or 2 weeks, reflecting the times that most patients can dedicate to thermal therapy. Patients were evaluated at baseline and end of treatment for psoriasis area and severity index (PASI) and body surface area; self-administered PASI (SAPASI) and Skindex-29 were evaluated at the same times, and also at 4 months by a mailed questionnaire. One-week balneotherapy or photobalneotherapy resulted in a significant reduction in PASI score (11.54% ± 2.76 and 12.76% ± 3.79, respectively; mean ± standard deviation; $p < 0.001$). Two-week therapy induced a greater response with photobalneotherapy than with balneotherapy alone, with PASI reduction of 19.8% ± 24.5 and 13.5% ± 23.1 ($p < 0.005$), respectively. These results were confirmed by SAPASI and Skindex-29 evaluation. The therapy was well tolerated. Skin improvement was mostly lost after 4 months. Short-term balneotherapy and photobalneotherapy could thus be offered to patients willing to temporarily discontinue pharmacologic therapy or as adjuvant therapy.

Studi in vitro



- per la prima volta in ambito nazionale è stata realizzata una ricerca sull'espressione in vitro di citochine da parte di cellule cutanee di pazienti psoriasici in coltura a cui veniva aggiunta acqua di Comano versus acqua ultra pura: l'acqua di Comano inibisce significativamente la produzione di citochine pro-infiammatorie

- studi eseguiti con colture cellulari hanno dimostrato che la balneoterapia causa inibizione-riduzione di molecole pro-infiammatorie espresse dalle cellule implicate nelle risposte immunologiche

Inibizione molecole pro-infiammatorie

- Chiarini A, Dal Pra I, Pacchiana R, Menapace L, Zumiani G, Zanoni M, Armato U. Comano's (Trentino) thermal water interferes with the expression and secretion of VEGF-A protein isoforms by cultured human psoriatic keratinocytes: a potential mechanism of its anti-psoriatic action. *Int J Mol Med* 2006;18:17-25.

- Chiarini A, Dal Pra I, Pacchiana R, Zumiani G, Zanoni M, Armato U. Comano's (Trentino) thermal water interferes with IL-6 production and secretion and with cytokeratin-16 expression by cultured human psoriatic keratinocytes: further potential mechanisms of its anti-psoriatic action. *Int J Mol Med* 2006;18:1073-9.

- Dal Pra I, Chiarini A, Pacchiana R, Zumiani G, Zanoni M, Armato U. Comano's (Trentino) thermal water interferes with **TNF-alpha** expression and IL-8 production and secretion by cultured human psoriatic keratinocytes: yet other mechanisms of its anti-psoriatic action. *Int J Mol Med* 2007;19:373-9.

Studi su animali da esperimento

INTERNATIONAL JOURNAL OF MOLECULAR MEDICINE 2012;29:732-40

Effects of thermal water on skin regeneration

PREMIO "MASSIMO VANNUCCI" 2013 istituito dalla fondazione per la ricerca scientifica termale (FORST) consegnato in una cerimonia ufficiale alla CAMERA DEI DEPUTATI.

STUDIO CASO-CONTROLLO SPERIMENTALE:

VERIFICARE L'ATTIVITA' RIGENERATRICE DELL'ACQUA TERMALE NELLA CICATRIZZAZIONE DI FERITE SUPERFICIALI

NUOVE INDICAZIONI TERAPEUTICHE=
riparazione di ferite dopo incidenti, ustioni e trattamenti estetici aggressivi

NOVITÀ: IL MICROBIOTA

PRIMO STUDIO A LIVELLO MONDIALE

SUL RUOLO DEL MICROBIOTA NELLA PSORIASI

…MA COS'È IL MICROBIOTA?

INTESTINO E PELLE

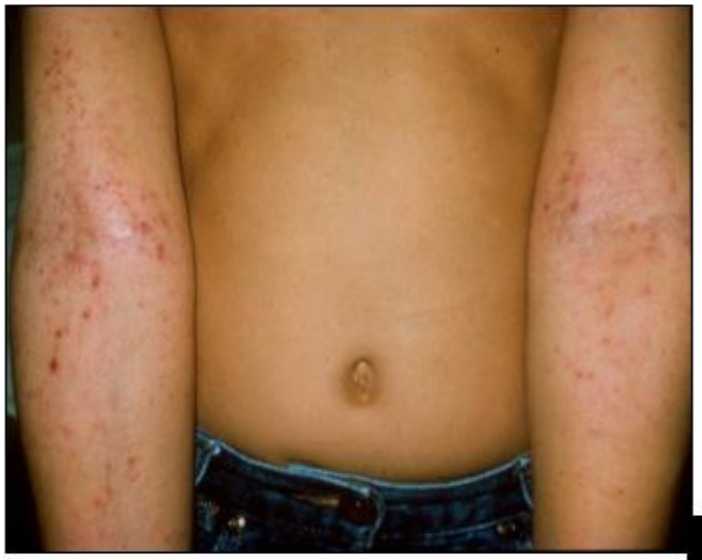
MICROBIOTA e DERMATITE ATOPICA

Eczema, immunity & the skin microbiome

Heidi H. Kong
Dermatology Branch, CCR, NCI

AD is a complex disease

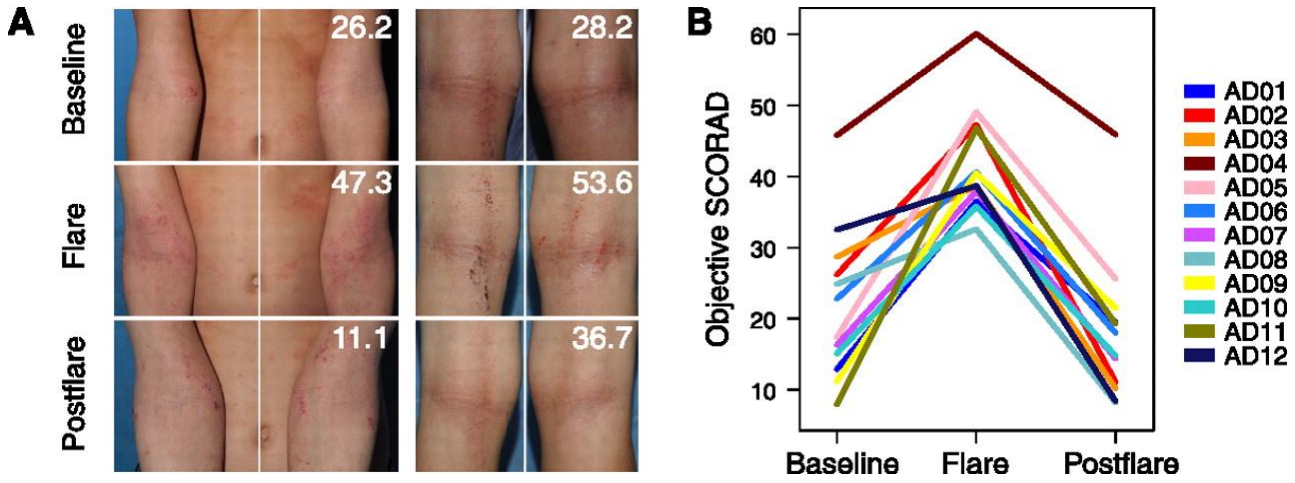
Skin Barrier (Filaggrin)

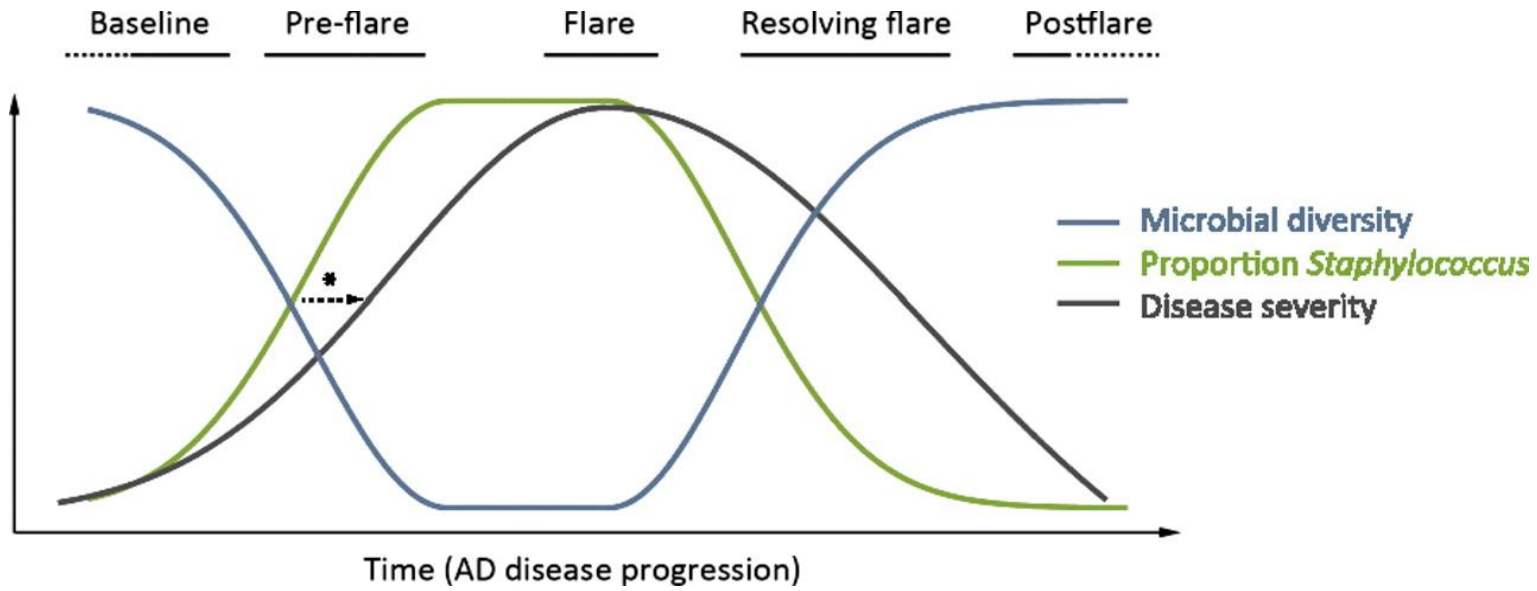


Immune System (IgE, AMP)

Microbes (*S. aureus*, viral infections)

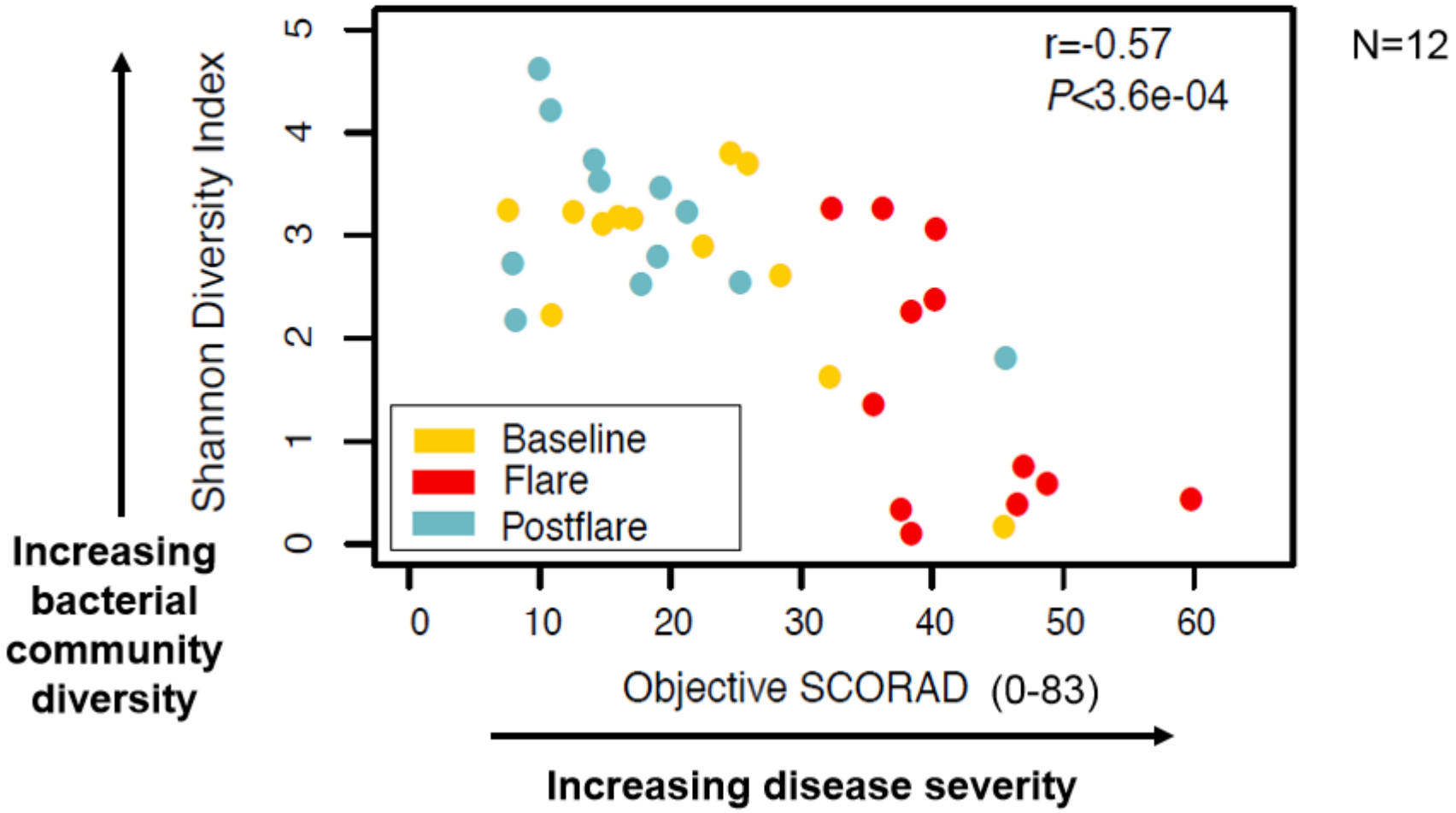
AD microbiome progression hypothesis





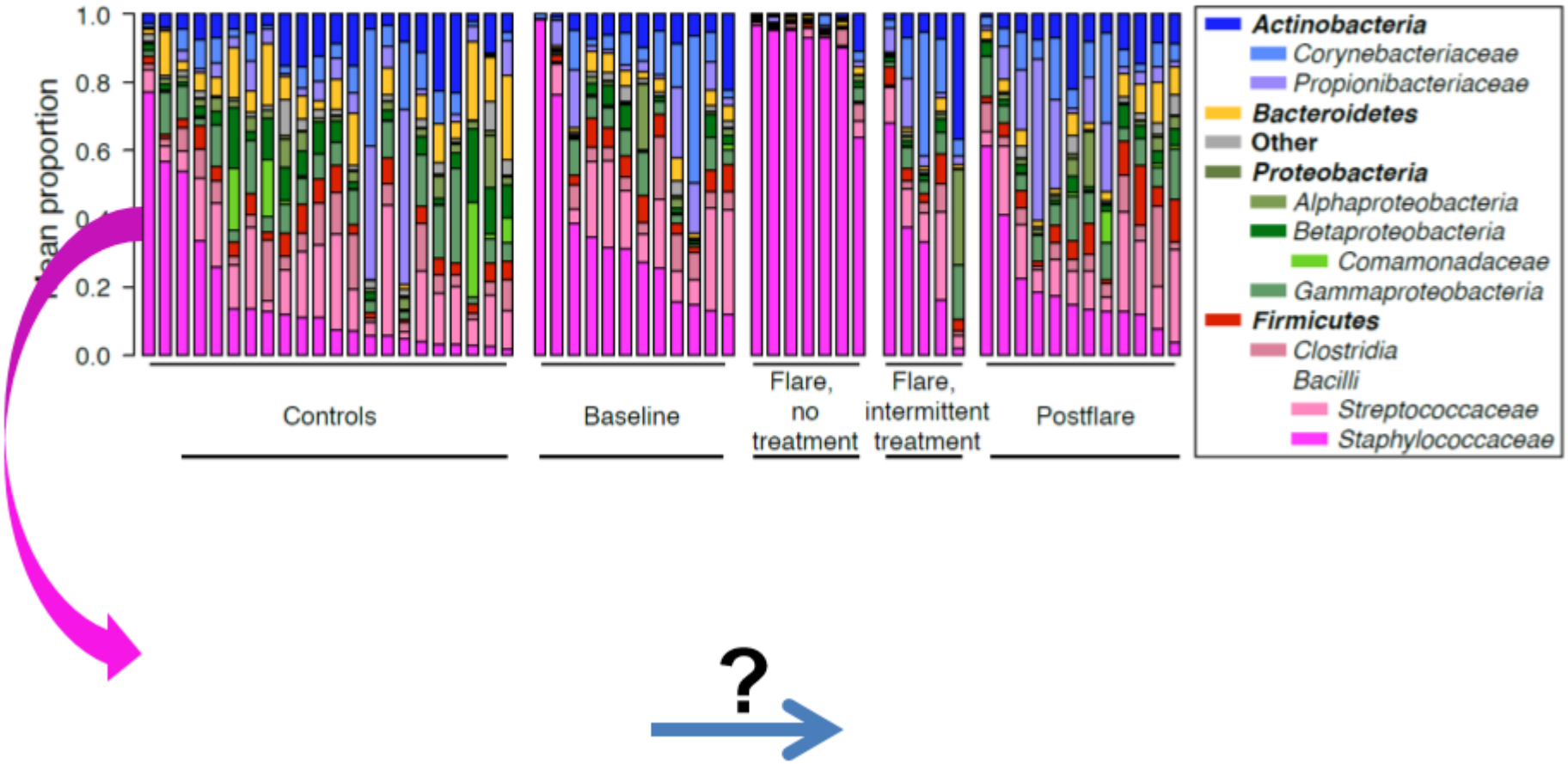
Kong et al. *Genome Res* 2012.

Skin bacterial diversity correlates with AD disease severity



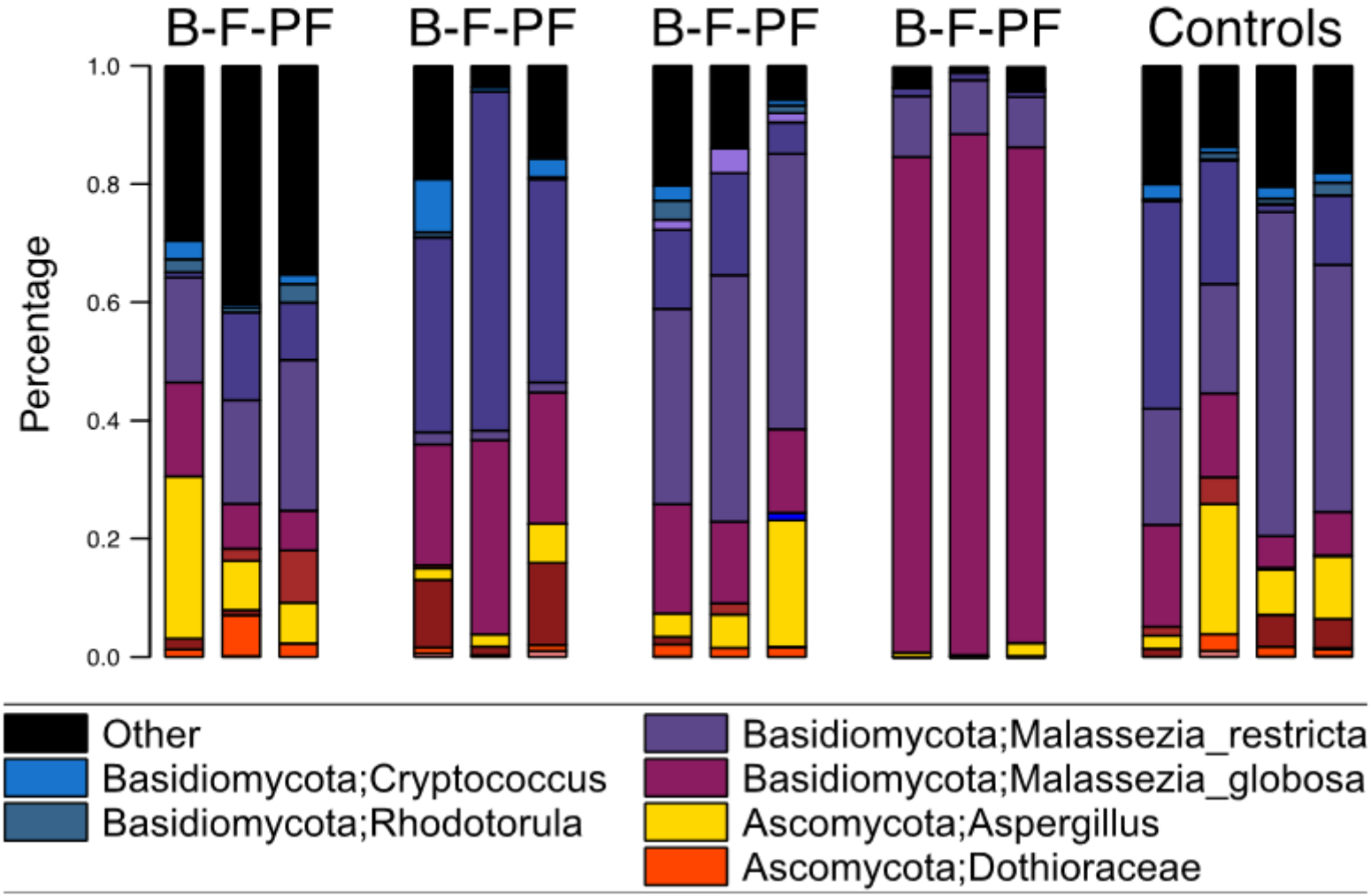
Kong et al. *Genome Res* 2012.

Staphylococcus spp increase during AD flares



Kong et al. *Genome Res* 2012.

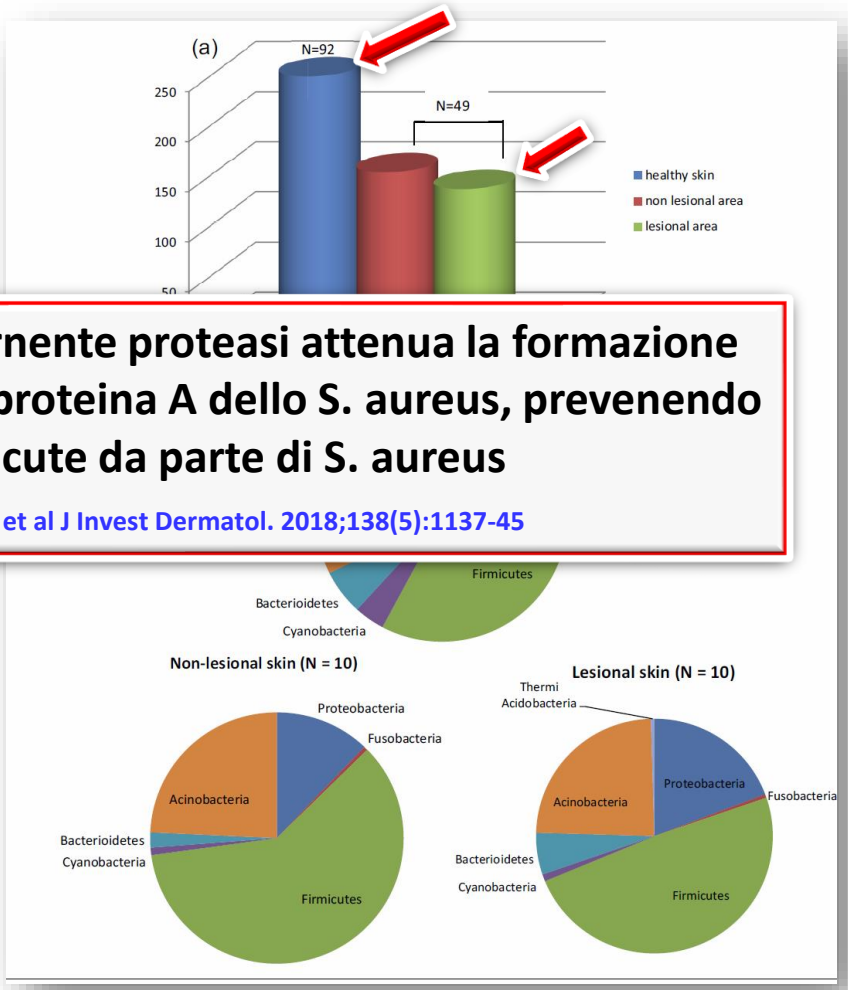
In contrast, fungal communities can be stable despite disease flares



unpublished

Modifiche diversità microbiche: cute sana vs DA

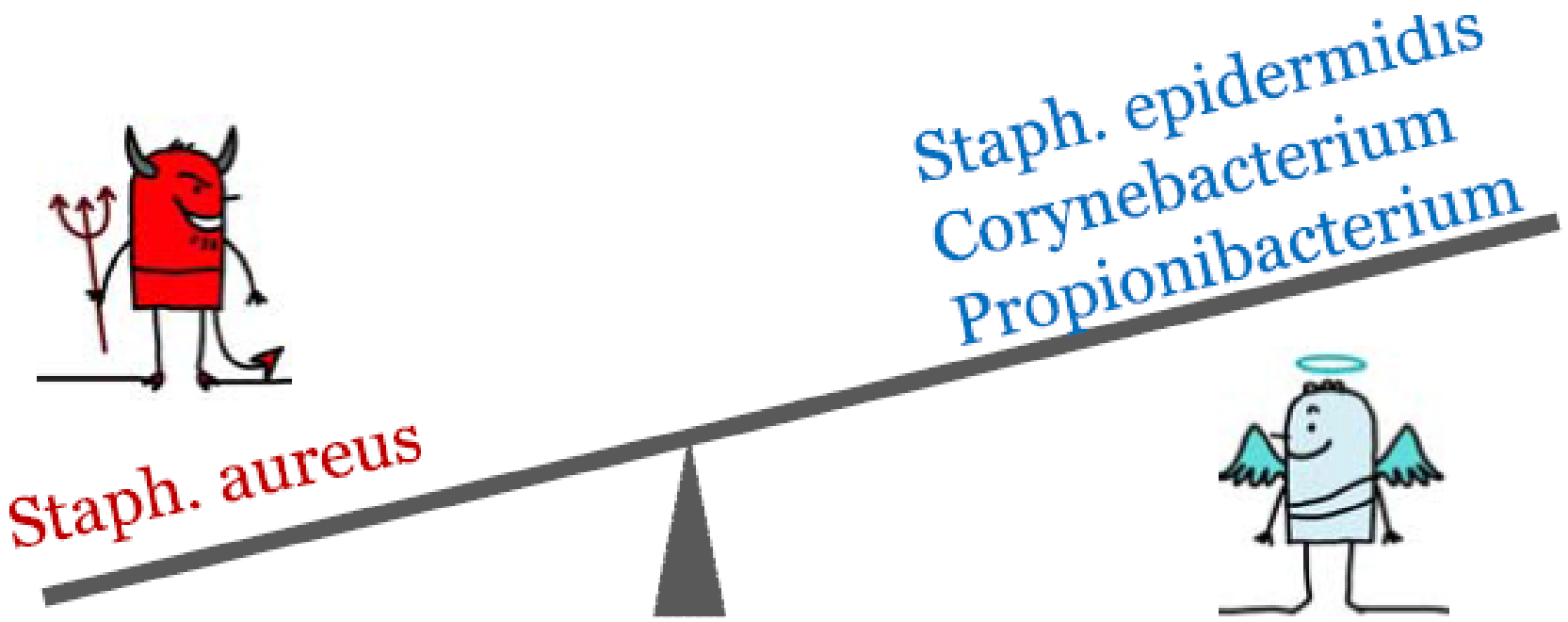
Normal skin atopic	Lesional skin
Actinobacteria (phylum)	
- *Corynecbacterium* (genus)	Decreased relative abundance
- *Propionibacterium* (genus)	
- *Rothia* (genus)	
- *Betaproteobacteria* (class)	
- *Gammaproteobacteria* (class)	
Firmicutes (phylum)	
- *Streptococcus* (genus)	Decreased relative abundance
- *Staphylococcus* (genus)	*Streptococcus/Granulicatella*
- *Granulicatella* (genus)	Increased absolute and relative abundance *Staphylococcus*



Il commensale cutaneo Malassezia globosa-secernente proteasi attenua la formazione del biofilm di S. aureus: è in grado di scindere la proteina A dello S. aureus, prevenendo la formazione di biofilm e la colonizzazione della cute da parte di S. aureus (meccanismo di difesa transazionale tra regni) Li H et al J Invest Dermatol. 2018;138(5):1137-45

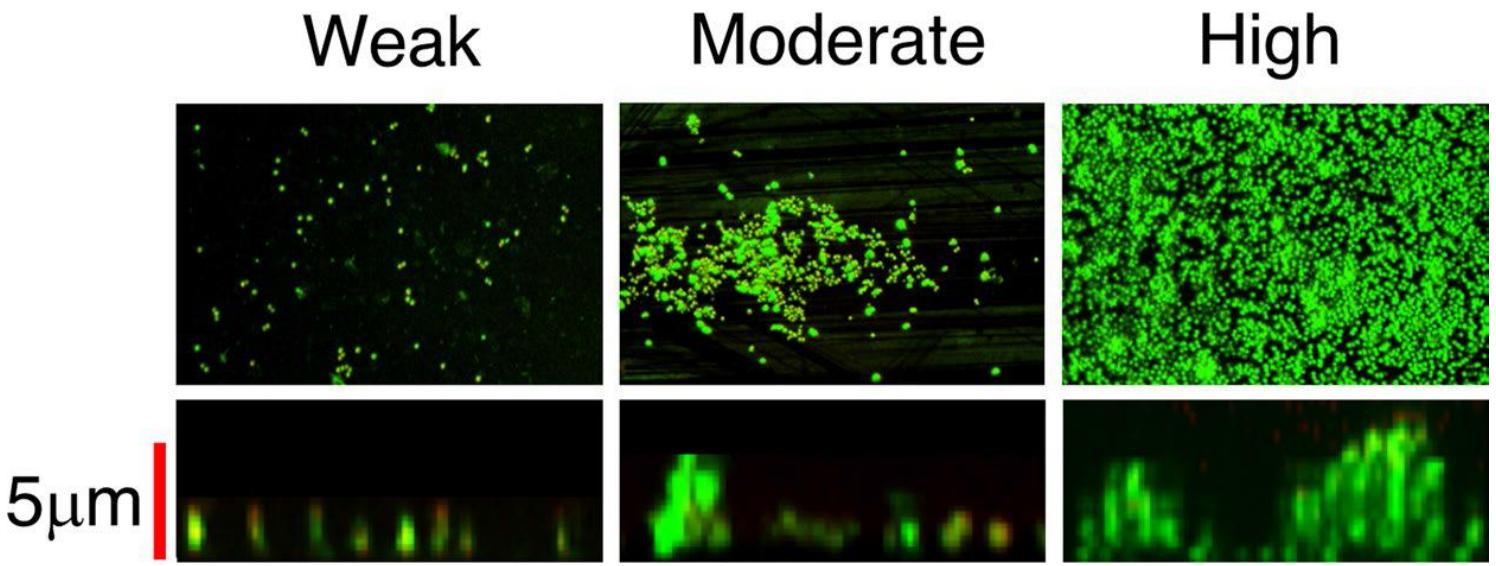
Williams MR,Gallo RL Curr Allergy Asthma Rep 2015; 15: 65

Paragone tra microbiomi sani e DA



La pelle sana è caratterizzata da una comunità polimicrobica. Nei pazienti con DA in fase di stato sono presenti comunità microbiche con più batteri «antistafilococco» che producono fattori che inibiscono la crescita dello S. aureo. Nelle fasi di riaccensione della DA lo S. aureo domina nella comunità microbica Odell IA et al Nat Microbiol 2016;1(9): 16135

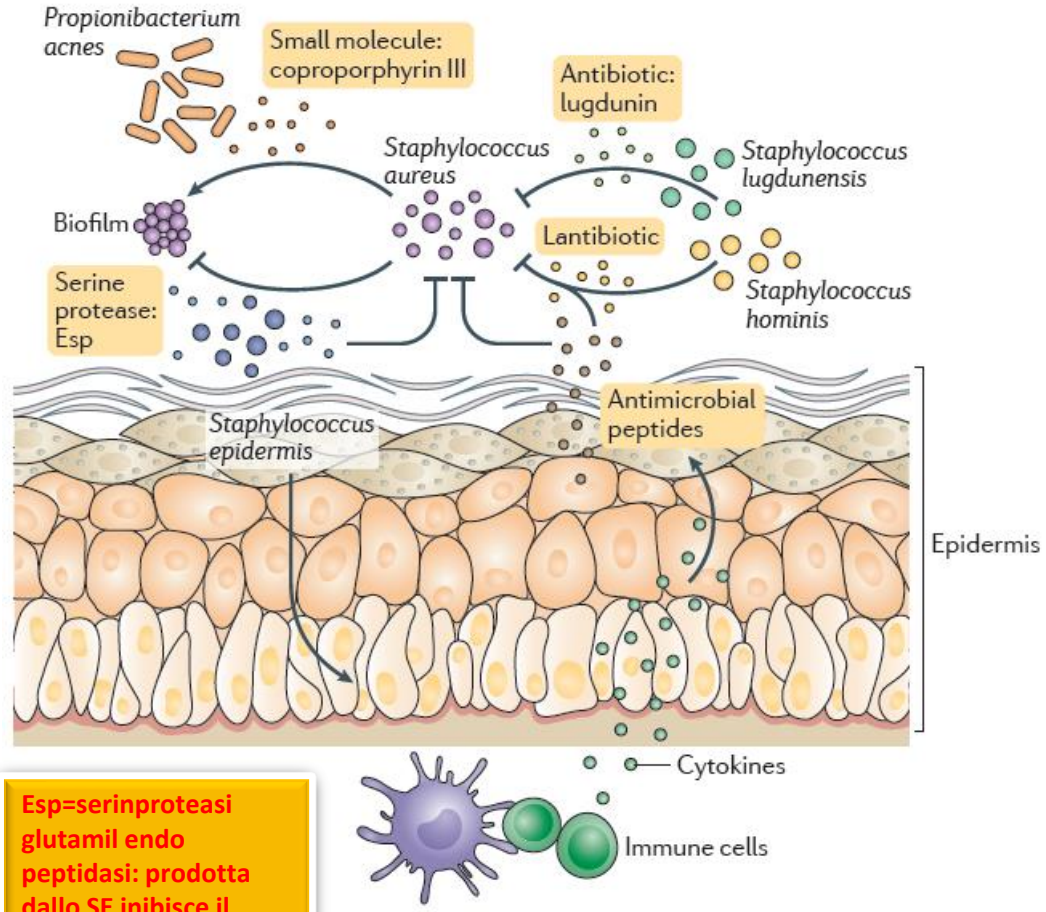
Gli SA ad alta produzione di biofilm sono associate con gravi forme di DA



Gli S. aureus isolati sono classificati in tre gruppi (deboli, moderati e alti) in base alla loro capacità di formare biofilm. Confrontando il grado di gravità delle lesioni cutanee con la capacità di produrre biofilm è emerso che il 60% dei pazienti con DA grave sono stati colonizzati da SA alti produttori di biofilm, il 35% da produttori di biofilm moderati e solo il 5% da produttori di biofilm deboli.

Di-Domenico EG et al Sci Rep. 2018 Jun 28;8(1):9573.

Interazioni dei commensali con S. aureo



Esp=serinproteasi glutamil endo peptidasi: prodotta dallo SE inibisce il biofilm dello SA

Byrd AL et al Nat Rev Microbiol. 2018 Mar;16(3):143-55

1. **S. coagulase neg Lugdunensis**
2. **S. epidermidis**
3. **S. hominis > Lantibiotici = LL-37 peptide antimicrobico umano**

In contrasto: P. acnes produce coproporfirina III che promuove l'aggregazione di S. aureus e la formazione di biofilm.

Lo S. aureus è in grado di attraversare l'epidermide e nel derma incontra le cellule immunitarie e innesca l'espressione di citochine infiammatorie es. IL-4, IL-13.

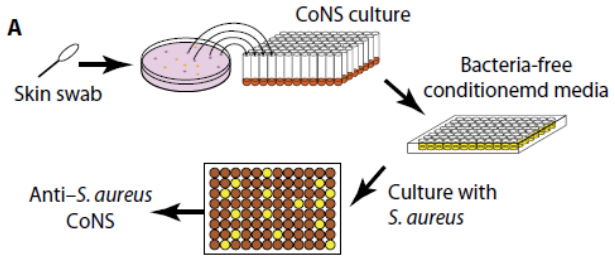
La capacità dello S aureo di innescare la risposta immunitaria cutanea può essere ceppo dipendente

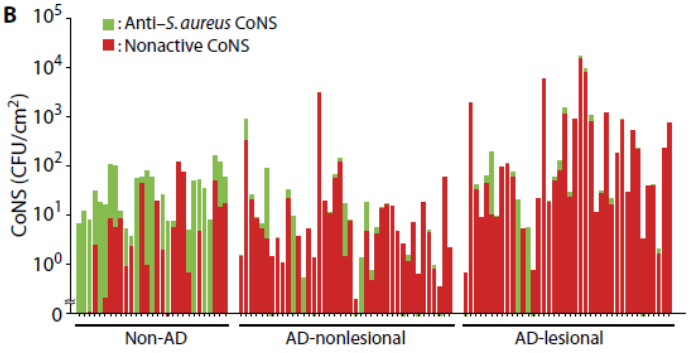
Byrd AL et al *Sci. Transl Med 2017*:9:eaal4651

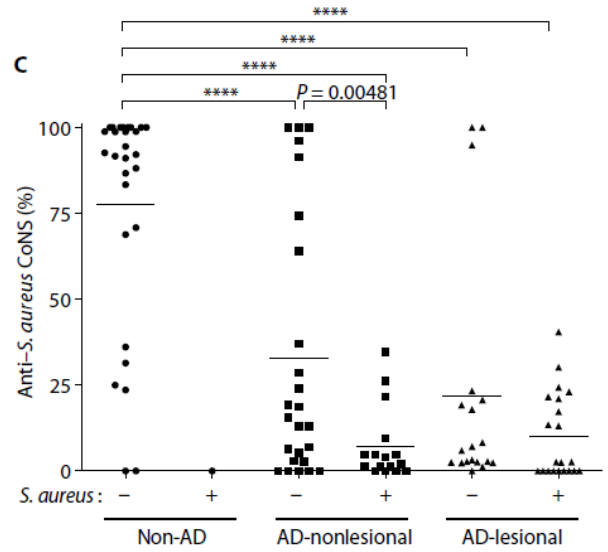
Ceppi di S. aureus isolati dalla cute infiammata di bambini e adulti con DA hanno evidenziato che i CC30 isolati sono sottorappresentati mentre i ceppi CC1 sono sovrarappresentati rispetto ai soggetti sani

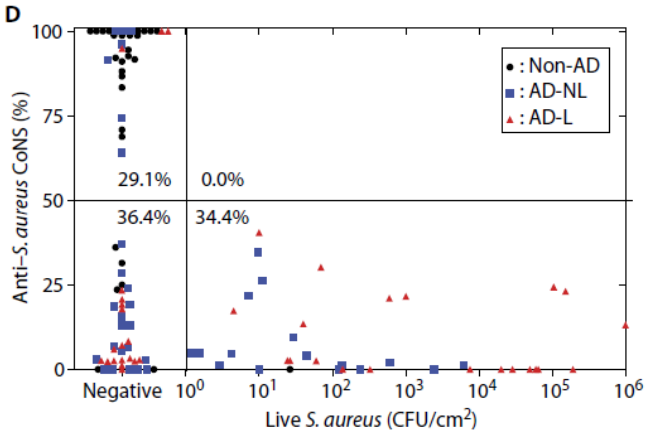
Sostanze antimicrobiche dei commensali proteggono contro S. aureo

- I … olazione r…
- L…) prodotti c…
- C… lo SA e s…
- L… umani c… iosi del r…







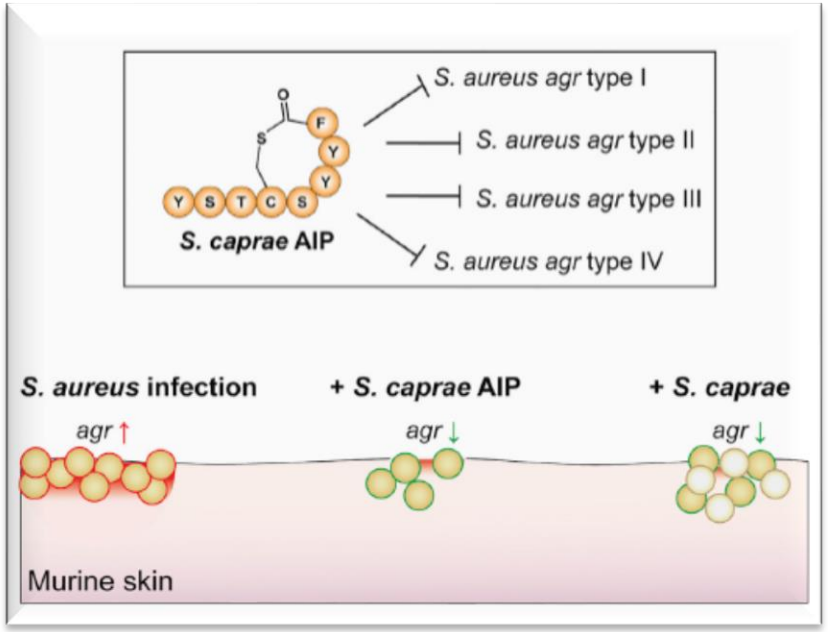


Nakatsuji T et al Sci Transl Med 2017;22:9(378)

Un ceppo di Stafilocco coagulasi negativo previene la colonizzazione di S. aureus bloccando il QUORUM SENSING

= linguaggio di comunicazione tra microbi ("sensibilità e controllo di livello"): i batteri producono molecole segnale (autoinduttori) che innescano reazioni cellula-cellula che permettono ai batteri di interagire

- **Il commensale S. caprae compete con SA inibendo il quorum sensing**
- **L'autoinduttore S. caprae (AIP) inibisce il quorum sensing per lo SA: S. caprae riduce il carico di SA resistente alla meticillina sia nella colonizzazione cutanea che nelle infezioni, evidenziando i benefici di una flora cutanea sana e suggerendo una nuova strada per la terapia probiotica**



Paharik AE et al Cell Host & Microbe 2017; 22: 1–11

CUTE SECCA NELLA DA

Nello strato corneo della cute dei pazienti con DA:

- ✓ **Livelli inferiori di sfingomielinasi della famiglia delle cerebrosidasi , un enzima necessario per la conversione degli sfingolipidi in ceramidi funzionali**

- ✓ **Diminuiti livelli di sfingosina che è dotata di un potente effetto antimicrobico contro lo *S. aureus* e potrebbe svolgere un ruolo importante nei meccanismi cutanei di difesa contro i batteri; più bassi livelli di sfingosina sono correlati con l'elevato numero di batteri, in particolare *SA*, presenti sulla superficie cutanea dei soggetti atopici**

- ✓ **Una riduzione della sintesi di acidi grassi poli-insaturi, in particolare i metaboliti di omega 3 (acido eicosapentaenoico o EPA e l'acido docosaesaenoico o DHA) e omega 6 (γ-linolenico e acido arachidonico)**

Emollienti e microbiota cutaneo

- **Alcune formulazioni di creme hanno una potenziale attività prebiotica poiché possono fornire cibo per il microbiota cutaneo**

FAO Technical Meeting Report on PREBIOTICS: Food Quality and Standards Service (AGNS) Food and Agriculture Organization of the United Nations (FAO);2008 http://www.aattaa.eu/index/en/company/download/1262610500.html

- **I prebiotici sono ingredienti e sostanze nutritive che stimolano selettivamente la crescita e l'attività dei batteri commensali**
- **I prebiotici che potrebbero essere inclusi nei prodotti per la pelle hanno anche il potenziale per supportare il mantenimento del microbiota cutaneo normale**

Al-Ghazzewi FH et al Benef Microbes 2014, 5(2): 99-107

Emollienti e microbiota cutaneo

- **Gli agenti emollienti es. ceramidi inclusi negli idratanti possono essere buone fonti di carbonio e azoto per i batteri**

- **La niacinamina (vitamina B3) è combinata con emollienti in alcuni prodotti della pelle ed è anche impiegata nei terreni di coltura per alcuni batteri. Può essere utile nel promuovere la salute della pelle poiché è stato dimostrato che inibisce la crescita di S aureus meticillino resistente**

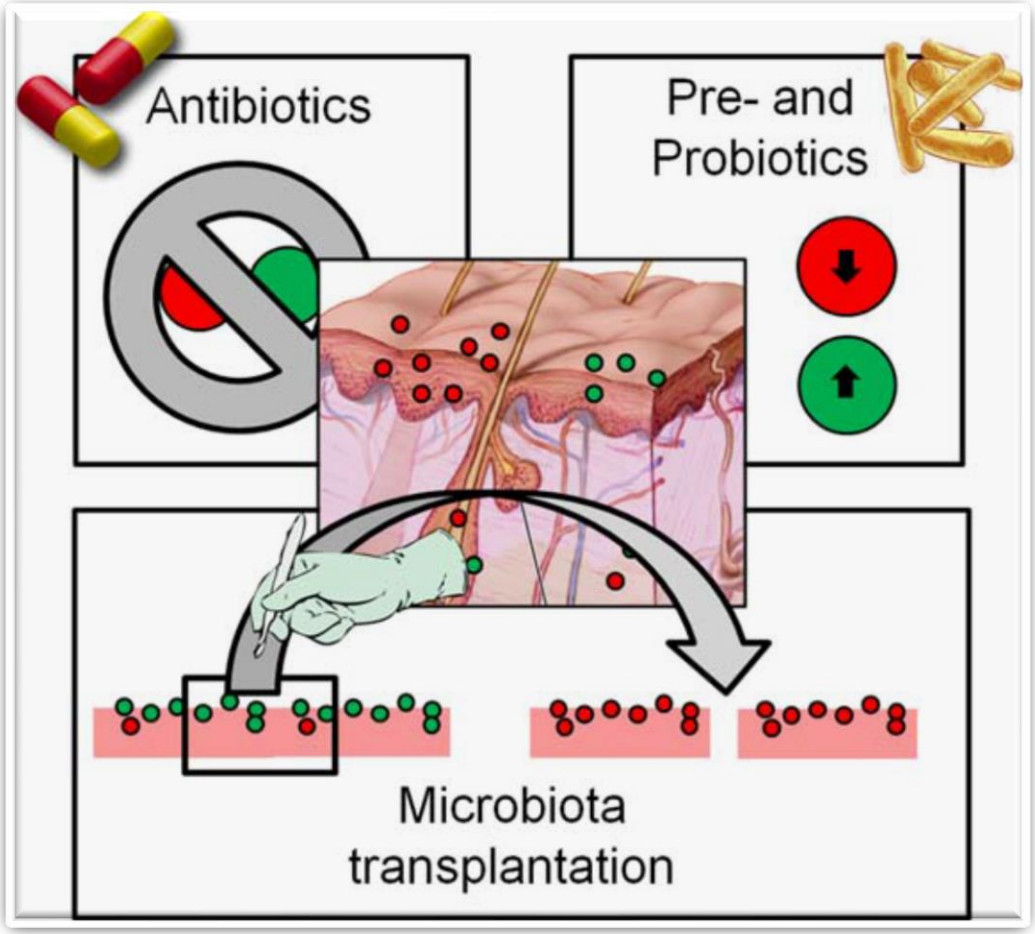
  Kyme P et al *J Clin Invest* 2012 Sep, 122(9): 3316-332925

- **Gli idratanti possono anche avere proprietà anti-infiammatorie con impatto potenziale sul microbiota cutaneo**

  Seite S et al Clin Cosmet Investig Dermatol 2015, 8: 479-4839

Modalità terapeutiche che agiscono sul microbiota

- **Prebiotici** (sostanze non digeribili che promuovono la crescita di batteri utili)
- **Probiotici** (batteri viventi e attivi)
- **Batteriofagi** (virus con attività antibatterica)
- **Trapianto**



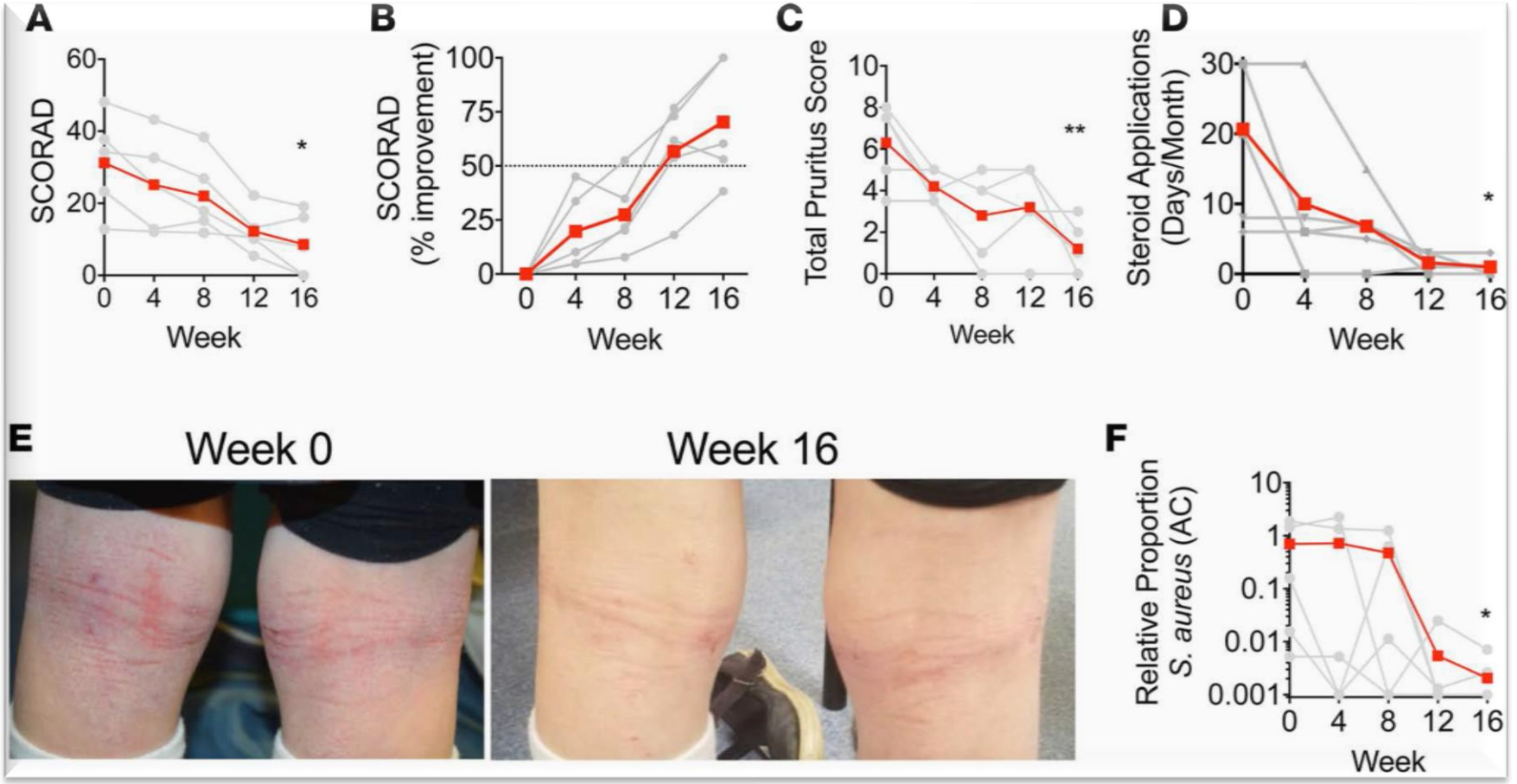
Musthaq S et al Clin Dermatol 2018 in press

STAPHEFEKT

- Una lisina di batteriofago (Staphefekt) è attualmente sottoposta a uno studio fase III come agente topico per il trattamento dell'eczema negli adulti
- I vantaggi della lisina rispetto all'acido fusidico sono:
  1. è rapidamente battericida
  2. è specifica per S. aureus
  3. è improbabile che si verifichi una resistenza durante il trattamento
- Staphefekt ha come target sia lo S. aureus meticillino-sensibile che meticillino-resistente, ma non interferisce con i microbi cutanei commensali e si prevede che NON induca resistenza batterica a causa del suo specifico meccanismo di azione

Tottè JEE et al Case Rep Dermatol 2017;9:19–25

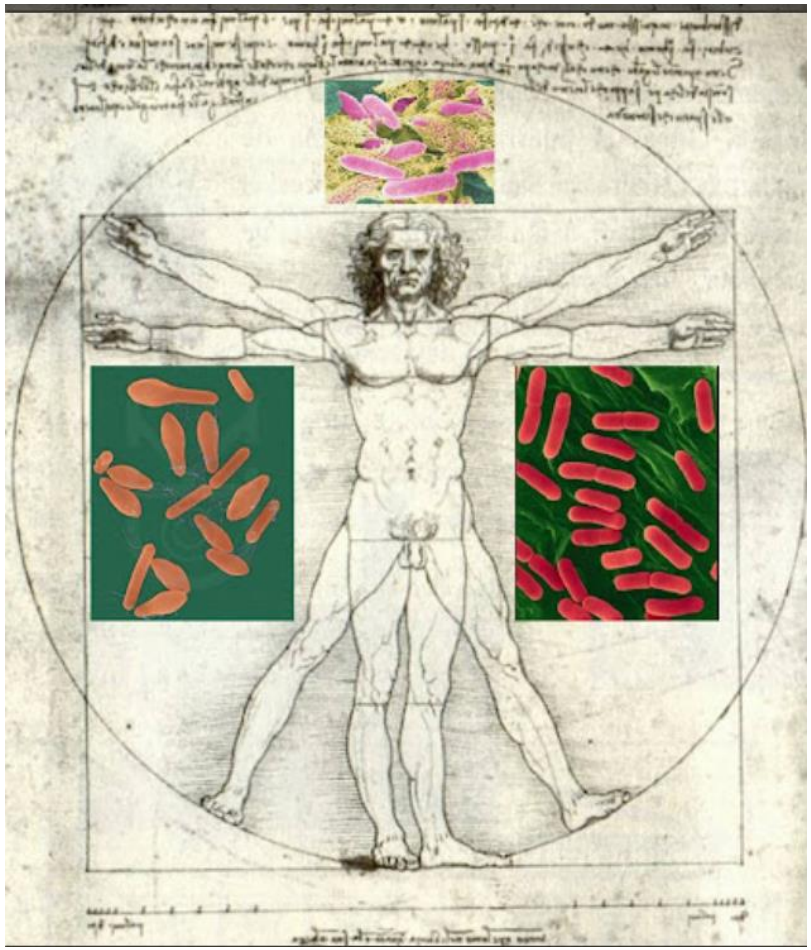
First-in-human topical microbiome transplantation with Roseomonas mucosa for AD



(F) **Ratio of Staphylococcus aureus to coagulase-negative staphylococci from the antecubital (AC) fossa as determined by culture**

Myles IA et al JCI Insight. 2018;3(9):e120608

MICROBIOTA E PSORIASI



Br J Dermatol 2013 Jul;169(1):47-52

Is chronic plaque psoriasis triggered by microbiota in the skin?

- **PSORIASI e MALATTIA DI CROHN >** disregolazione della tolleranza immunitaria verso il microbiota dell'intestino (individui geneticamente predisposti)

- **Streptococchi** beta-emolitici implicati nella **psoriasi guttata**

- **Sistema immunitario innato** si attiva nella psoriasi e molti geni associati con la malattia sono implicati nelle vie di segnalazione del sistema immunitario innato, in particolare di IL23/Th17 e NFkB

PSORIASI: DISREGOLAZIONE DELLA TOLLERANZA IMMUNITARIA NEI CONFRONTI DEL MICROBIOTA DELLA PELLE

PLOS ONE

RESEARCH ARTICLE

Intestinal Microbiota Promotes Psoriasis-Like Skin Inflammation by Enhancing Th17 Response

Abstract

Psoriasis is a chronic inflammatory skin disease in which Th17 cells play a crucial role. Since indigenous gut microbiota influences the development and reactivity of immune cells, we analyzed the link among microbiota, T cells and the formation of psoriatic lesions in the imiquimod-induced murine model of psoriasis. To explore the role of microbiota, we induced skin inflammation in germ-free (GF), broad-spectrum antibiotic (ATB)-treated or conventional (CV) BALB/c and C57BL/6 mice. We found that both mice reared in GF conditions for several generations and CV mice treated with ATB were more resistant to imiquimod-induced skin inflammation than CV mice. The ATB treatment dramatically changed the diversity of gut bacteria, which remained stable after subsequent imiquimod application; ATB treatment resulted in a substantial increase in the order *Lactobacillales* and a significant decrease in *Coriobacteriales* and *Clostridiales*. Moreover, as compared to CV mice, imiquimod induced a lower degree of local and systemic Th17 activation in both GF and ATB-treated mice. These findings suggest that gut microbiota control imiquimod-induced skin inflammation by altering the T cell response.

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PSORIASIS (J WU, SECTION EDITOR)

The Role of the Skin and Gut Microbiome in Psoriatic Disease

Di Yan[1] · Naiem Issa[2] · Ladan Afifi[1] · Caleb Jeon[1] · Hsin-Wen Chang[1] · Wilson Liao[1]

Abstract

Purpose of Review To understand the changes in the microbiome in psoriatic disease, we conducted a systematic review of studies comparing the skin and gut microbiota in psoriatic individuals and healthy controls.

Recent Findings Our review of studies pertaining to the cutaneous microbiome showed a trend towards an increased relative abundance of *Streptococcus* and a decreased level of *Propionibacterium* in psoriasis patients compared to controls. In the gut microbiome, the ratio of *Firmicutes* and *Bacteroidetes* was perturbed in psoriatic individuals compared to healthy controls. *Actinobacteria* was also relatively underrepresented in psoriasis patients relative to healthy individuals.

16s rRNA

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METHODS REVIEW (INVITED)

WILEY Experimental Dermatology

Experimental metagenomics and ribosomal profiling of the human skin microbiome

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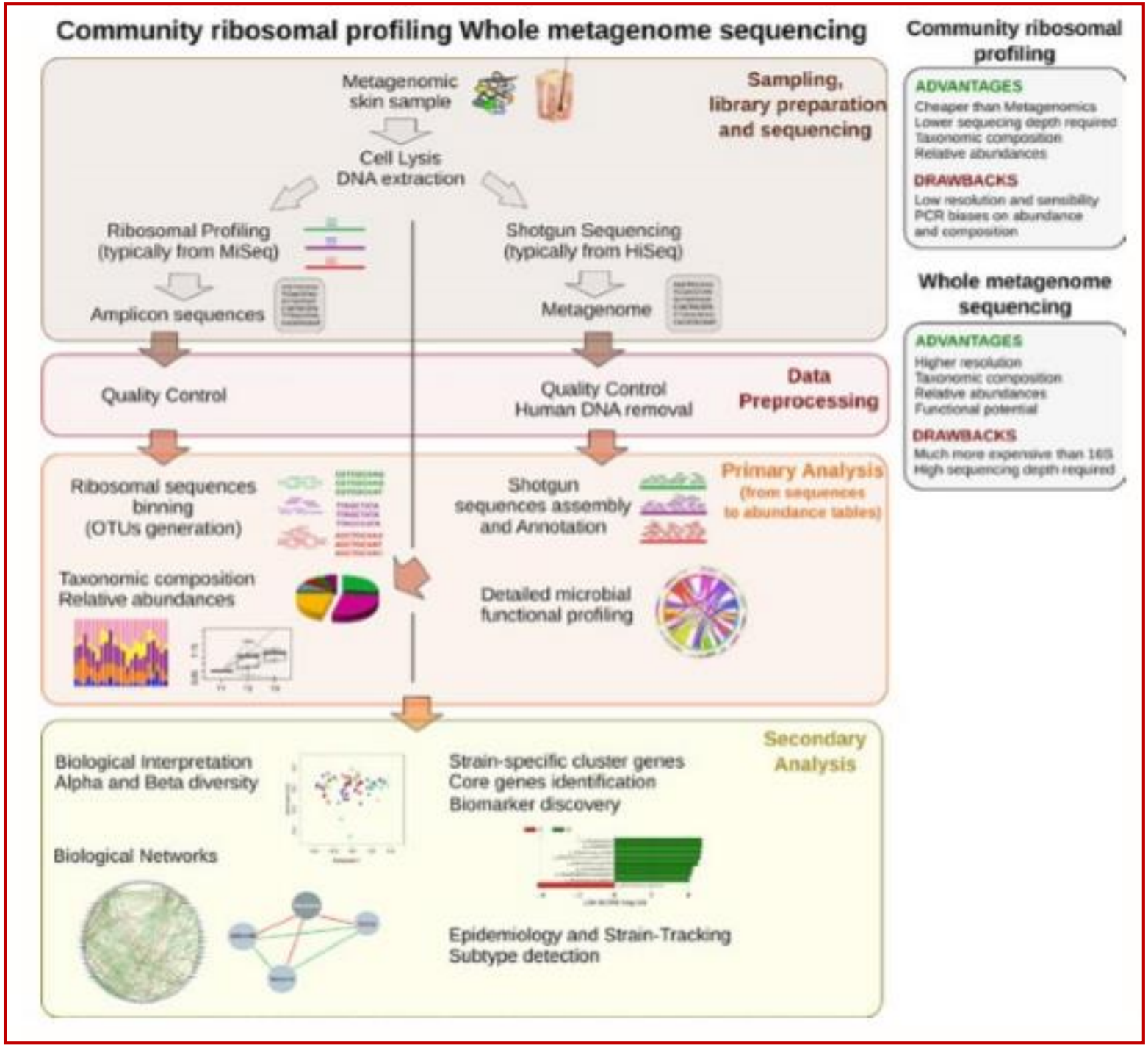
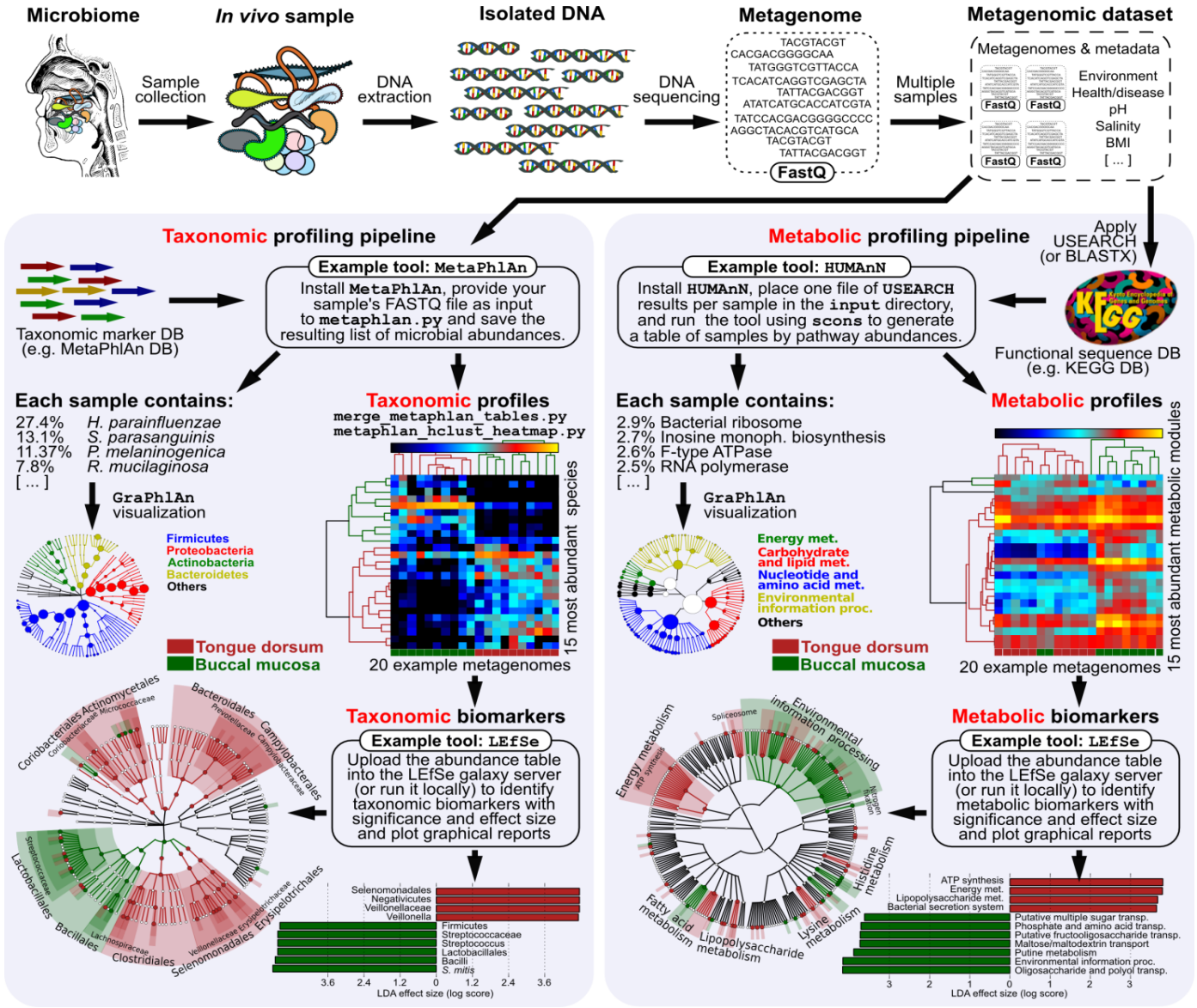
Abstract

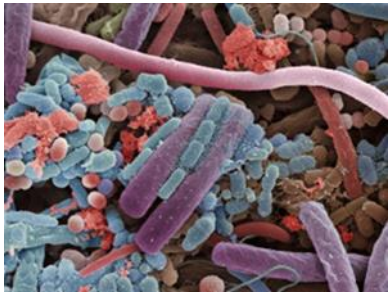
The skin is the largest organ in the human body, and it is populated by a large diversity of microbes, most of which are co-evolved with the host and live in symbiotic harmony. There is increasing evidence that the skin microbiome plays a crucial role in the defense against pathogens, immune system training and homoeostasis, and microbiome perturbations have been associated with pathological skin conditions. Studying the skin resident microbial community is thus essential to better understand the microbiome-host crosstalk and to associate its specific configurations with cutaneous diseases. Several community profiling approaches have proved successful in unravelling the composition of the skin microbiome and overcome the limitations of cultivation-based assays, but these tools remain largely inaccessible to the clinical and medical dermatology communities. The study of the skin microbiome is also characterized by specific technical challenges, such as the low amount of microbial biomass and the extensive human DNA contamination. Here, we review the available community profiling approaches to study the skin microbiome, specifically focusing on the practical experimental and analytical tools necessary to generate and analyse skin microbiome data. We describe all the steps from the initial samples collection to the final data interpretation, with the goal of enabling clinicians and researchers who are not familiar with the microbiome field to perform skin profiling experiments.


Community ribosomal profiling Whole metagenome sequencing
Metagenomic skin sample
Sampling, library preparation and sequencing
Cell Lysis DNA extraction
Ribosomal Profiling (typically from MiSeq)
Shotgun Sequencing (typically from HiSeq)
Amplicon sequences
Metagenome
Quality Control
Quality Control Human DNA removal
Data Preprocessing
Ribosomal sequences binning (OTUs generation)
Shotgun sequences assembly and Annotation
Primary Analysis (from sequences to abundance tables)
Taxonomic composition Relative abundances
Detailed microbial functional profiling
Secondary Analysis
Biological Interpretation Alpha and Beta diversity
Strain-specific cluster genes
Core genes identification
Biomarker discovery
Biological Networks
Epidemiology and Strain-Tracking
Subtype detection
Community ribosomal profiling
ADVANTAGES
Cheaper than Metagenomics
Lower sequecing depth required
Taxonomic composition
Relative abundances
DRAWBACKS
Low resolution and sensibility
PCR biases on abundance and composition
Whole metagenome sequencing
ADVANTAGES
Higher resolution
Taxonomic composition
Relative abundances
Functional potential
DRAWBACKS
Much more expensive than 16S
High sequencing depth required

BIO-INFORMATICA



CASE STUDY: the skin microbiome of the elbow as seen by shotgun metagenomics



CONCLUSIONS AND PERSPECTIVES

- The **recent advances** in high- throughput methodologies and the continuous **reduction in the cost** of sequencing have opened **new frontiers** in microbial ecology by dramatically broadening the discovery potential of skin-related research studies.
- The **metagenomic approach** provides unprecedented means to understand and describe in a comprehensive way the complex interaction networks underlying **the host- skin microbiome symbiosis and dysbiosis.**
- We described here the basic experimental and analysis **procedures to perform skin microbiome studies** summarizing the current state of the art of a subfield of dermatology that we foresee will be of **crucial relevance in the next few years.**

npj | Biofilms and Microbiomes

www.nature.com/npjbiofilms

ARTICLE OPEN

Unexplored diversity and strain-level structure of the skin microbiome associated with psoriasis

Adrian Tett[1], Edoardo Pasolli[1], Stefania Farina[2], Duy Tin Truong[1], Francesco Asnicar[1], Moreno Zolfo[1], Francesco Beghini[1], Federica Armanini[1], Olivier Jousson[1], Veronica De Sanctis[3], Roberto Bertorelli[3], Giampiero Girolomoni[4], Mario Cristofolini[2] and Nicola Segata[1]

Psoriasis is an immune-mediated inflammatory skin disease that has been associated with cutaneous microbial dysbiosis by culturedependent investigations and rRNA community profiling. We applied, **for the first time, high-resolution shotgun metagenomics** to characterise the microbiome of psoriatic and unaffected skin from 28 individuals. We demonstrate psoriatic ear sites have a decreased diversity and psoriasis is associated with an increase in Staphylococcus, but overall the microbiomes of psoriatic and unaffected sites display few discriminative features at the species level. Finer strain-level analysis reveals strain heterogeneity colonisation and functional variability providing the intriguing hypothesis of psoriatic niche-specific strain adaptation or selection. Furthermore, we accessed the poorly characterised, but abundant, clades with limited sequence information in public databases, including uncharacterised Malassezia spp. These results highlight the skins hidden diversity and suggests strain-level variations could be key determinants of the psoriatic microbiome. This illustrates the **need for high-resolution analyses**, particularly when identifying therapeutic targets. This work provides a baseline for microbiome studies in relation to the pathogenesis of psoriasis.

npj Biofilms and Microbiomes (2017)3:14 ; doi:10.1038/s41522-017-0022-5

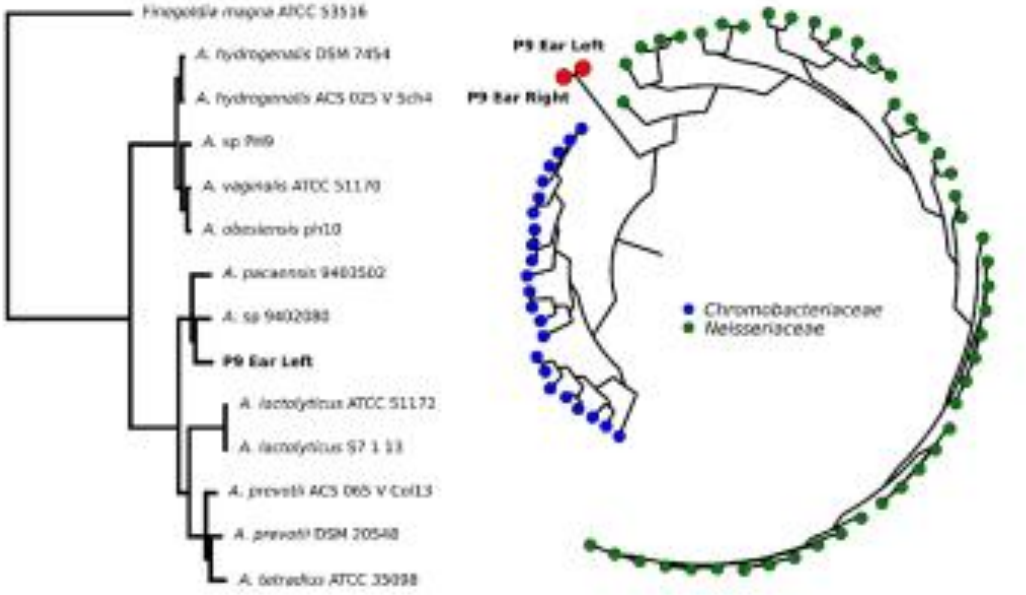
MICROBIOTA PSORIASI

- BATTERI + PARTICELLE VIRALI E CELLULE FUNGINE

  > alcune delle quali appartenenti a specie microbiche

  senza genomi sequenziati e **non ancora descritte**

Uncharacterized organisms in Psoriasis



L'analisi a livello di ceppo

dei batteri più abbondanti

(*Staphylococcus epidermidis* e

Propionibacterium acnes)

sembra evidenziare

specificità a livello di sottospecie

sia per ogni singolo individuo

che per la nicchia ecologica

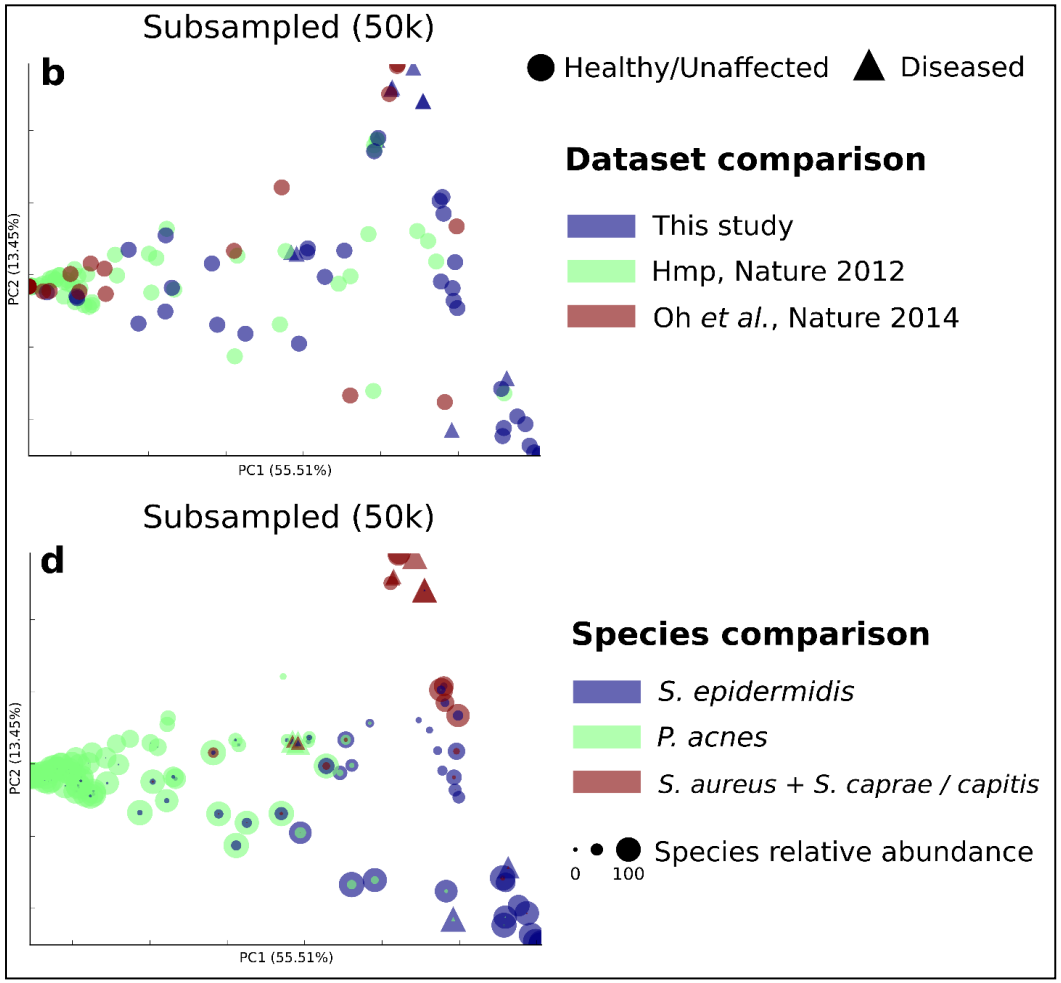
indotta dalla psoriasi

3 TIPOLOGIE DI MICROBIOTA CUTANEO

1. **S epidermidis**
2. **P acnes**

} **cute sana**

3. **Altro** = poca abbondanza di S epidermidis e P acnes → **cute malata**



PSORIASI
3° GRUPPO

> servono più campioni!

POTENZIALE STRATEGIA TERAPEUTICA=
spingere verso primi due gruppi…

Gold Award dalla LEO Pharma Research Foundation nel 2015 a Rotterdam all'ESDR (European Society for Dermatological Research)

Gold Award Winner Lecture

"Metagenomics of the Skin: Results and Perspectives on our Microbial Interface"

Dr. Nicola Segata (Trento)

MICROBIOTA E TERME

Terme di Comano

> **STUDIO LONGITUDINALE PRE-POST TRATTAMENTO**

PSORIASI
DERMATITE ATOPICA

RICERCA IN CORSO

TAMPONI CUTANEI
CAMPIONI FECALI

TERME OSPEDALE

Progetto dello studio

Visita PRE-POST TRATTAMENTO

TERME= 12 bagni (idropinica; fototerapia)
OSPEDALE= 2 settimane di farmaci topici da linee guida

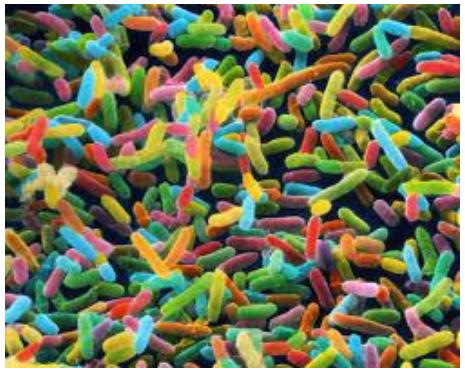
PSO= 18-65 aa, 1 gomito malato, no farmaci da 15 gg
DA= 3-12 aa, 1 piega antecub. malata, no farmaci da 15 gg

TAMPONI CUTANEI= 4 + 4 (8 per pz)
CAMPIONI FECALI= 1 + 1 (2 per pz)

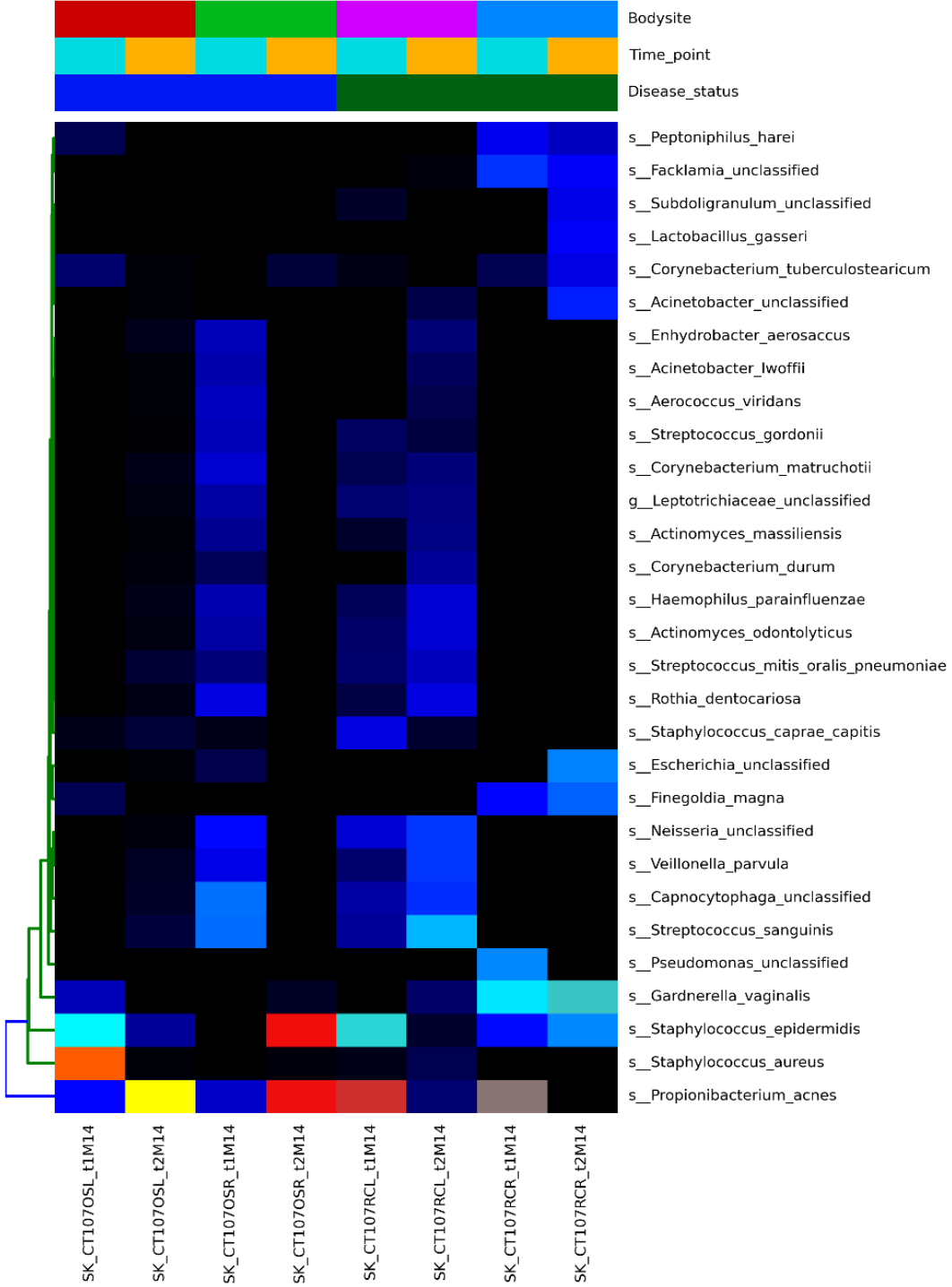
DATI ANAMNESTICI, STILE DI VITA
PASI E SCORAD + BSA

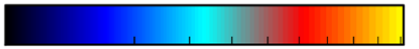
MICROBIOTA E TERME

- Il trattamento termale è in grado di riequilibrare il microbiota cutaneo alterato nelle malattie della pelle?
- E’ questo il meccanismo d’azione alla base delle documentate proprietà immunoregolatrici delle acque termali?



Risultati preliminari P107 TERME





Time_point
1
2

Bodysite
Left_Elbow
Right_Ear
Right_Elbow
Left_Ear

Disease_status
Yes
No

8 CAMPIONI: 4 PRE 4 POST

GOMITO SX > P acnes
GOMITO DX > P acnes e S ep.

Nella parte sana no!

PASI 6 > PASI 2 (12 bagni)
F 34 aa (15), BMI 23, no PsA

Conclusioni

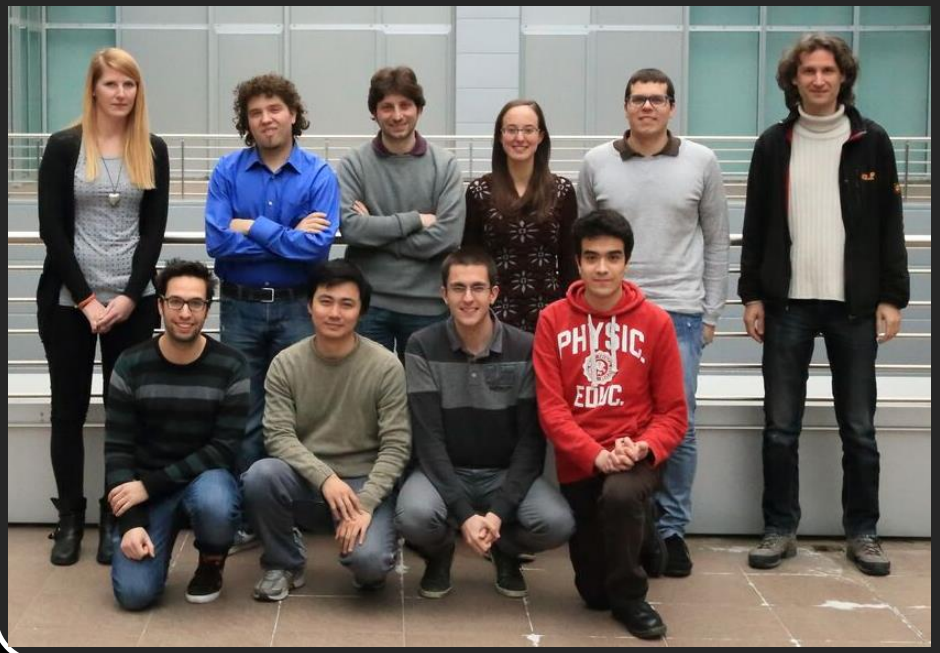
1) Confermare il ruolo del microbiota nelle MALATTIE DELLA PELLE

2) Confermare il ruolo del microbiota nell' EFFICACIA DELLE CURE TERMALI

3) Confrontare il ruolo terapeutico dell'acqua termale rispetto ai farmaci tradizionali nel MODULARE IL MICROBIOTA CUTANEO senza turbarne l'equilibrio

Thanks!

The Laboratory of Computational Metagenomics



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ISTITUTO
G.B. MATTEI
RICERCA IN IDROLOGIA MEDICA
E MEDICINA TERMALE

CIBIO

TERME DI COMANO

Azienda Provinciale
per i Servizi Sanitari
Provincia Autonoma di Trento