

Added Value on Sade Village and Bau Nyale Festival in Autoimmune Diseases Immunization Travel: Supported by Aptamers Technology

Peni K Samsuria Mutalib¹, Mirna Nurasri Praptini², Mutalib Abdullah³, Meny Hartati⁴

¹Department of Medical Physics, Faculty of Medicine, Universitas Indonesia, INDONESIA

²Department of Internal Medicine, Gatot Subroto Hospital, Jakarta, INDONESIA

³Unit Hemodialysis, Department of Internal Medicine, Tangerang District General Hospital, Banten, Universitas Indonesia, INDONESIA

⁴Departement of Pathology Anatomy, Faculty of Medicine, University of Indonesia, INDONESIA.

Abstract—Prevalence of Autoimmune diseases (AD) are high in developed countries and low in developing countries. Wall of worm were associated with lower level of allergy and support the hygiene hypothesis (HyHy). Long term use of Interferon as drug for AD and synthetic vaccine made by epitope mapping are global economic burden. Adolescence from developed countries traveling to Ghana forwarding AD-HyHy. Fecal microbiota transplantation (FMT) for fighting AD have been developed in hygiene countries such as UK, Japan and Korea, meanwhile the aims of this study are reveal an added value to Sade village 'FMT culture' and Bau Nyale/Mandalika Princess festival for Nature Vaccination on AD. These local nature vaccination needs to be known by policy maker and political doer and could be a translational-medicine education topic to lessen AD economic global burden. Method: Systematic-review and Bayesian network analysis. EBSCO host search engine were used. Result: Description of 9 Publications of meta-analysis are chosen. Conclusions: The increasing of immunity in developing countries and decreasing in clean habit educated family is based on hygiene hypothesis, could be answered by local life-style and festival. These added value for local tour package has been supported by affirmers and aptamers contemporary technology based on bacteria and worm epitope mapping.

Keywords—hygiene hypothesis-autoimmune diseases, bacteria and worm cell wall, aptamers, epitope mapping, Fecal Microbiota Transplantation (FMT).

I. INTRODUCTION

Wall of worm cell have many epitope as well dormant bacteria (Fecal Microbiota Transplantation or FMT),¹⁻⁵ is now locally neglected and globally abandoned. Usage of natural antigen for vaccination is hygiene hypothesis (HyHy) based on prevention such as in allergy epidemic in US.⁶⁻⁸ Decreasing autoimmune disease (AD) by natural AD vaccination as added value of Sade and Bau Nyale festival, could lessen AD burden. Meta-analysis on Rheumatoid Arthritis (RA) molecule has ethnicity relation⁹ parallel with new loci RA in Japan^{10,11} and Korean and European eight new RA risk loci.¹¹ Meta-analysis on FMT in IBD¹² and hygiene lifestyle are associated with allergic, atopic sensitization,⁷ and asthma. Hand vs. machine dishwashing have significantly different AD prevalence.¹³ A number of references show that AD and climate^{14,15} and socioeconomic status¹⁴ are related to HyHy.^{8,16} Do these factors contribute to the occurrence of increasing prevalence of AD in developed countries? Meanwhile, protocols in synthetic vaccine industry for AD or treatment strategies for people with AD, with interferon longterm usage are still unclear. No publication before that summarizes and describes the association of HyHy, AD, FMT, Genome Wide RA,¹⁷ RA in developed countries,¹⁸⁻²⁰ Epitope-RA-SLE,²¹ Helminth-Hygiene-AD,^{22,23} vaccine-epitope/antigen.^{22,24-26} Just by implementing local wisdom such as Sade village and Bau Nyale-Mandalika Princes festival can lower risk of AD. Effective preventive activities and treatments could be initiated for high risk person's AD caused by clean habit of living.^{6,13,27-31} This prevention and therapy model is the first effective natural vaccination idea published.

II. MATERIAL AND METHOD

Systematic review and Bayesian network analysis using EBSCOhost search engine. The search was performed up to Sept 2016 in 3 steps. First, searching with Google search engine for the definition of known key words, then with CINAHL plus with full text for developing the knowledge for the aims of study. Using the following search terms: Autoimmune Diseases, Hygiene Hypothesis, Epidemiology and AD, Atopic Sensitization, Asthma, T1D, IBS, MS, Rheumatoid Arthritis, Ulcerative

Colitis, Allergic Diseases. AD AND Meta-Analysis (372), high prevalence in UK (Epidemiology and AD and UK (237), Japan (247), Korea (51). Low in Sierra Leone (0, SL ancestor (1), Egypt (0), Ghana (0). Where FMT are growing in high prevalence 3 countries, FMT (554), FMT AND UK (14), FMT AND Japan (12), FMT AND Korea (9). In molecular level using terms of: exposure of unhygienic bacteria, worm, epitope with some topics: high in tropical rainforest area (wet and warm) and savana dry and warm climate; combination of worm antigen-prevent T1D³²; Epitope E. coli-vaccine³³; wet and warm countries: Ghana¹⁴; making of synthetic vaccination HBV aptamers: next generation sequencing³⁴; synthetic long peptide vaccine²⁴; long peptide synthetic vaccines with just one protective epitope²²; FMT for extra-intestinal disorders AD³⁵ (FMT industrialization)³⁵. recent therapy and education on HyHy: Exposure 1: sade village cultural: bacteria and parasitic cell wall as natural ligand³; Exposure 2: bau nyale-putri mandalika cultural event (annelids) : Effect of helminth-induced immunity on infections,³⁶ : helminth can protect IBDS, an Meta-analysis (MA)³⁶; Schistosoma induce Treg³⁷; Ghana: Longitudinal studies increase in immunological disorders as it grew cleaner³⁷; helminth therapy for allergy³⁹; probiotic-helminth¹; the ability of countries to respons of infectious and chronic diseases⁴⁰; lower prevalence on asthma and allergies in childhood exposed to infections, as postulated in the HyHy to fight AD⁴¹; School children in the beginning and the end of rainy season: wake up of dormant cell (April-October is the dry season) in Flores could be the Next Prevention on Autoimmune and TB vaccine⁴²: Immunizations by Traveling.

In the second Step, searching for meta-analysis of 2 key words related to the researcher Okada and Orenstein and one key words of helminth AND Autoimmune; EBSCO:CINA HL plus (Medline/PubMed) for FMT-MA (12), Helminth AND AD (137), Worm AND AD (33), Worm AND HyHy (17); Epitope AND Helminth AND Vaccine (80); and _in the molecular level_RA (Epidemiology AND MA AND RA (28.). All are Screening abstract or title: excluded the not relevant and the duplicates by Bayesian analysis. Since we were interested in explanatory factors of bacteria and worm epitope sequencing are filtered.

In the third step, screening full text publications, excluded since not relevant and publications has been filtrated for table 1. The selection was mainly performed by one reviewer and confirmed by the co-authors.

III. RESULTS AND DISCUSSIONS

3.1 Discussion

From clinical to molecular clue of inflammation markers in savanna (warm and dry climate) with dormant bacteria and worm in dry season, and also in tundra (cold and dry) where no worm no bacteria in all season are searched by us. Meanwhile AD have been found in low prevalence in wet and warm or hot and humid countries, whereas epidemic in clean countries. Dormant bacteria in dry season are specific physics-chemistry antigens and broad spectrum of variable microbiota implies rich of epitope of protein from known FMT. Fig. 1 and Table 1. showed the association of HyHy-allergy and AD.^{3,6-8,13-15,22,24,32,35,36,39,42,43} Whereas deepest understanding of inflammation reaction increase correlation with the generation of antibody and affimers based product based product induced by antigen based on epitope mappng⁵¹⁻⁵⁶ Immune Modulation and Prevention of Autoimmune Disease by Repeated Sequences from Parasites Linked to Self Antigens has reported.⁵⁶

Studies that have developed FMT and helminth probiotic for prevention and therapy of these diseases¹, and has been supported by recent studies,^{32,43,56} The association of Epitope mapping of similarity structure and the size length to the making of immunological properties has been reported⁵⁷⁻⁶⁰ Reduced Asthma produced from early childhood exposure is relied in developing country.⁶¹ Clean habit has support these AD and any potential association between bacteria and helminth infection.³⁵ In Sade village area which peoples expose to dormant bacteria and Bau Nyale cultural event in which sea-worm were catch to eat, prompt us to propose a specific HyHy to explain how dormant bacteria and helminth wall cell play a role as good antigen similar to high technology for making vaccine and antibiotics. Basically, using small or length peptide sequence from parasites has been an industrial economic income.^{22,24,35,46} People resistant from AD and the broad range of bacteria and worm might have contributed to the uprising national economic income for the most common infectious diseases burden countries like Ghana and Indonesia.^{38,40,42,55} With the recognition that FMT as well treatment for ulcerative colitis due to supported by epitope mapping-immunology technologies, and parallel with urban rich-urban poor epidemiology,⁶²⁻⁶⁴ Traveling to Sade village and participate in Bau Nyale-Mandalika princess festival will be good for AD patients, family, tribe and country with high prevalence of atopic sensitization, asthma, IBD, SLE, MS, psoriasis, Rheumatoid Arthritis.^{9,13,15,16,29,40,49,55,61,65}

TABLE 1
DESCRIPTION OF 9 IDENTIFIED LITERATURES ON META-ANALYSIS IN AD-FMT-GENOME WIDE VERY SIMILAR-EPIOTOPE-ONE SHOOT VACCINE-PRIMARY THERAPEUTIC AGENT

Study	Variables of Interest	Adjustment for other variables	Comparative risk measures for HyHy	Influence of co-morbidities	Influence of infectious and worm parasite
Okada 2016 ⁹	Ethnic Rheumatoid Arthritis Molecule	Ethnology, genetics, metabolism	Genome-Wide Association	Hygiene Hypothesis of Autoimmune Diseases	In Human meta-analysis
Sakai Bizmark 2016 ⁶⁴	Autoimmune in Developing countries	Asthma, allergic diseases World wide	Industrialized countries in Childhood	More prevalent in affluent countries	Epidemiology reduce in developing countries
Shi 2016 ⁶⁵	FMT	Efficacy Safety	Ulcerative colitis	Clinical remission	Clinical response
Lopez-Isac 2016 ⁴⁴	Genome wide RA Systemic Sclerosis	same direction, opposite-direction	Allelic effect Rheumatoid Arthritis	Incl. several genomic regions identified T1 Interferon and IL-12	Usefulness of a cross-disease GWAS meta-analysis strategy in the identification of common risk loci
Burr 2010 ⁶³	Rheumatoid Arthritis UK vs. Asian	RA in an independent group of RA cases and control	PADI4_94 Anti-CCP ab PTPN22	-	R PADI4-RA In Asian pop but no R in European ancestry
Dieguez-Gonzalez 2008 ²¹	Epitope Meta-analysis RA and SLE	ACPAs anti-citrullinated protein antibodies -vs.+	Rs2004640 IRFS Shared epitope OR 0.88 vs. controls	Very similar in SLE	OR haplotype 1.8 vs. controls, protective haplotype OR 0.76 vs. controls
Gorman 2004 ²⁹	Epitope Meta-analysis RA	SE shared epitope	Erosive disease in many ethnic groups OR 2.0; Greek)R0.8, South Eu Caucasians 6.2, Asians OR 5.4 with 2 SE alleles	Genetic and environmental differences in the clinical expression of RA	DRB1*0401 frequency among different ethnic group
Colman 2014 ¹²	FMT Meta-analysis	Primary therapeutic agent for IBD	Donor selection and microbiome analysis	Ulcerative Colitis, Crohn's diseases	Clinical remission and or mucosal healing
Orenstein 2014 ⁴⁹	Vaccine IBD	Additional diseases	Supply and delivery	Improving global health one shot at a time	Particularly in developing countries

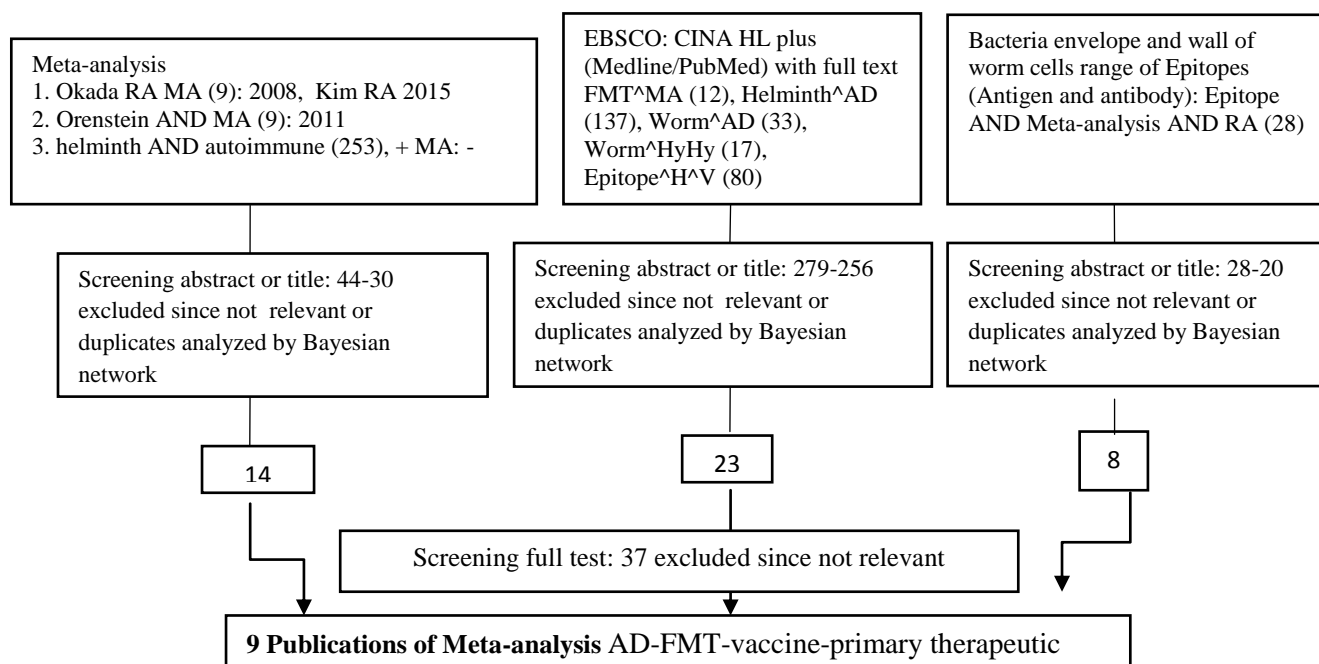


FIGURE 1. FLOWCHART OF THE IDENTIFIED LITERATURE
 RA: Rheumatoid Arthritis; MA: Meta-analysis; ^: AND`

The historic antibody level in developing countries is closely associated with worm enteric infection and in the other hand the emerging allergic epidemic is associated with low exposure of epitopes. In 2015, AD affects up to 50 million Americans, according to the American Autoimmune Related Diseases Association has 80 types, 70% women, and in the last few decades increase in the global prevalence.³⁹ A better comprehension of the association between helminthes and allergies is pressing as research orientation progress closer to harnessing the preventive potential of worms and derivational relations in also allergic disorders therapy.³⁹

The body produces Antibody against some of own tissue is the definition of AD. Epidemiology of T1D¹⁶ and AD to geography⁸ vs. HyHy³², helminth infection has associated negatively with AD^{5,14,23,39,42,43} has proven that geography and HyHy associate with socioeconomic status. FMT associate with AD was in HyHy topic,¹⁶ where as helminth associate with AD was in Epitope mapping topic.^{9,57,58,60} The increasing of inflammation cytokine associated with AD is also reveal in Anti TNF antibody; anti TNF-a treatment response in RA has been reported⁶⁶ and supported by others.^{43,56,67}

The same trends of HyHy-AD association in developing countries is proven in schoolchildren,³⁸ whereas animal studies demonstrated that worm antigens increase the protective effect and represent a new potential management therapy fighting AD.³³ The use of pills of frozen microbiota are already used in clinical trials, will be effective as the leading for abundant use and large industrialization of FMT.³⁵ These pills of frozen microbiota are similar with dormant bacteria in dry and hot area like Sade village, which is forbidden done in early rainy season where the dormant bacteria become active living bacteria (*pageblug/* epidemic disease). Synthesis vaccine of HBV are produce by Aptamer AND miRNA (43 publications). Aptamer AND vaccine (23); aptamer AND antibiotic (54); vaccine AND epitope (6941); antibiotic AND epitope (135) are found with EBSCOhost search engine. Treatment of several AD with worm and worm eggs mitigate the clinical symptoms and inhibited production of proinflammation cytokines and increase anti-inflammatory cytokines.⁴³ The hopes of creating vaccine based on new protective antigens not only for AD, but also in TB vaccine.⁴⁷ Vaccination for Mycobacterium tuberculosis⁴⁷ and antimicrobial peptides for vaccine nanolipoprotein have been reported^{24,25} but for AD were already answered by meta-analyses³⁶; and supported by others in table 1. Since 2010, de-Graft⁴⁰ convinced the double burden of infectious and chronic diseases which is a risk by FMT diversity microbiota but could be safe in Sade village and Bau Nyale festival. It is eastern to Wallace's Line, between tropical rainforest area (Bali island, humid and hot) and Savanna area (Sumbawa Island, dry and warm). One shot contemporary vaccine challenges could be improving global health vaccine, at a time,⁴⁹ cross diseases⁴⁴ and same IRF5 polymorphisms could influence RA similar to SLE patients.²¹

3.2 Bacterial and Parasite wall

Prevention of AD with immune modulation using repeated sequences from parasites associated to anti TNF or decrease TNFa associate with T cell epitope in RA Therapy known as affimer technology,⁶⁶ and Jhonson 2012⁵¹ made affimer which linked with impedance CRP immunoassay and TNFa.^{43,51,56,67} An intestinal worm infections longitudinal studies and allergy in rural vs. semi urban areas of Flores, Indonesia have been reported,⁴² which could help develop evidence-based policy making.⁴²

FMT beyond intestinal disorders,²² is supported by allergy reduction due to increase microbial exposure.¹³ Caucasian RA were lower than Japanese, which is statistically significant in the Japanese population¹⁵ by HyHy approach could now be simply understood. Another autoimmune reaction associate preeclamsia-EBV epitope⁵⁴ and the global multimorbidity pattern in multi country has been made.⁵⁵ Epitope mapping of tuberculosis antigen,⁵⁷ and other epitope mapping,⁵⁸ could now be help by Mass Sepctrometric epitope mapping⁵⁹ and short non-epitop vs. epitope prediction antibody binding,⁶⁰ but FMT is an effective therapy for recurrence CDI reduce the cost effectiveness therapy for CDI,⁵⁰ Qualitative and quantitative antigen induce immune responses,² and a linear surface epitope in a proline rich reg of HeV could be a model.⁴ Invariant NKT cells on Parasitic HyHy and cell wall of Bacterial and Parasit is a cellular structure in variety highly enriched of glycolipids and lipoprotein, is a cross talk of Th1, Th2, Th17, Treg, innate lymphoid cells.³

IV. LIMITATION

These Systematic review has several limitation 1) Non published literature on Sade village and bau nyale/princess Mandalika may limit the validity of our findings, but these cultural indigenous study are a real phenomenon which is already attracted peoples from developed and clean countries with AD burden. However, we used meta-analysis with partly overlapping data bases for our literature search on bacteria and worm cell wall antigens. And we found a large number of papers fulfilling the criteria of our search in these HyHy-AD prevention, diagnosis and therapeutic. 2) Another potential problem in this systematic review is that studies mainly used in the searching steps are depended on the vocabulary synonyms (not find in

general, but many in specific such as autoimmune diseases could be Rheumatoid arthritis, recurrent CDI, IBS, T1D, atopic sensitization, asthma etc.). Different chances changes choices used give different results may be misleading. We intended to manage this problem in an additional work, by dividing the using chosen specific to generic into 2 broad categories: measurements and epidemiological findings.

V. CONCLUSION

Epitope of FMT, dormant bacteria, protein from the wall of worm are all rich of ranges epitopes and could be present in cultural event like Sade village and Bau Nyale 'Mandalika princess' festival. These indigenous study from local, present to global is similarly paralleled with epitope mapping and contemporary industrial affirmers and aptamers based on epitope biotechnology for diagnostic, vaccination and therapeutic fighting against autoimmune diseases. Further education to policy maker and global politic doer from local to global will support this added value idea.

ACKNOWLEDGEMENTS

We thank DRPM University of Indonesia, for the funding of specific stuff exposure in wet and warm/ hot and humid climate DRPM UI 2015 no. 1772/UN2.R12/HKP.05.00/2015 and 240BE/DRPM-UI/NI.4/2008 and IMERI 2016 abstract send no. 5229. To dr. Adhi Midjadja, Pediatrician who works as a hospital director, dr. Sulasno, Anesthetist who lives in Lombok, and dr. Mardiatmo, Radiologist, also works as hospital director, we thank for supporting the poster presentation.

DISCLOSURE

All authors have no potential conflict of interest. The study received financial support from DRPM University of Indonesia.

REFERENCE

- [1] Fleming JO, Isaak A, Lee JE, Luzzio CC, Carrithers MD, Cook TD, et al. Probiotic helminth administration in relapsing-remitting multiple sclerosis: a phase 1 study. *Mult Scler* 2011;17(6):743–54.
- [2] Yang D, Frego L, Lasaro M, Truncali K, Kroe-Barrett R, Singh S. Efficient Qualitative and Quantitative Determination of Antigen-induced Immune Responses. *J Biol Chem* 2016;291(31):16361–74.
- [3] Yang J-Q, Zhou Y, Singh RR. Effects of Invariant NKT Cells on Parasite Infections and Hygiene Hypothesis. *J Immunol Res* 2016;2016:2395645, 9 pages
- [4] Yang Y, Lin S, Nan Y, Ma Z, Yang L, Zhang Y. A Linear Surface Epitope in a Proline-Rich Region of ORF3 Product of Genotype 1 Hepatitis E Virus. *Viruses* 2016;18;8(8).
- [5] Ding Y, Zhou R, Yang X, Zhang L. [The Role of Adoptive Transfer of Immune Cells in Helminth- induced Regulation of Allergy and Autoimmune Diseases]. *Zhongguo Ji Sheng Chong Xue Yu Ji Sheng Chong Bing Za Zhi* 2015;33(4):290–4.
- [6] Shunsheng Han C. A specific hygiene hypothesis. *Med Hypotheses* 2016;93:146–9.
- [7] Lynch SJ, Sears MR, Hancox RJ. Thumb-Sucking, Nail-Biting, and Atopic Sensitization, Asthma, and Hay Fever. *Pediatrics* 2016;138(2) e20153983
- [8] Figueiredo CA, Amorim LD, Alcantara-Neves NM, Matos SMA, Cooper PJ, Rodrigues LC, et al. Environmental conditions, immunologic phenotypes, atopy, and asthma: new evidence of how the hygiene hypothesis operates in Latin America. *J Allergy Clin Immunol* 2013;131(4):1064.
- [9] Okada Y, Raj T, Yamamoto K. Ethnically shared and heterogeneous impacts of molecular pathways suggested by the genome-wide meta-analysis of rheumatoid arthritis. *Rheumatology (Oxford)* 2016;55(1):186–9.
- [10] Okada Y, Terao C, Ikari K, Kochi Y, Ohmura K, Suzuki A, et al. Meta-analysis identifies nine new loci associated with rheumatoid arthritis in the Japanese population. *Nat Genet* 2012 Mar 25;44(5):511–6.
- [11] Kim K, Bang S-Y, Lee H-S, Cho S-K, Choi C-B, Sung Y-K, et al. High-density genotyping of immune loci in Koreans and Europeans identifies eight new rheumatoid arthritis risk loci. *Ann Rheum Dis* 2015;74(3):e13–e13.
- [12] Colman RJ, Rubin DT. Fecal microbiota transplantation as therapy for inflammatory bowel disease: a systematic review and meta-analysis. *J Crohns Colitis* 2014;8(12):1569–81.
- [13] Hesselmar B, Hicke-Roberts A, Wennergren G. Allergy in Children in Hand Versus Machine Dishwashing. *Pediatrics* 2015;135(3):e590–7.
- [14] Obeng BB, Amoah AS, Larbi IA, de Souza DK, Uh H-W, Fernández-Rivas M, et al. Schistosome infection is negatively associated with mite atopy, but not wheeze and asthma in Ghanaian schoolchildren. *Clin Exp Allergy J Br Soc Allergy Clin Immunol* 2014;44(7):965–75.
- [15] Okada Y, Mori M, Yamada R, Suzuki A, Kobayashi K, Kubo M, et al. SLC22A4 polymorphism and rheumatoid arthritis susceptibility: a replication study in a Japanese population and a metaanalysis. *J Rheumatol* 2008;35(9):1723–8.

- [16] Chatenoud L, You S, Okada H, Kuhn C, Michaud B, Bach J-F. 99th Dahlem conference on infection, inflammation and chronic inflammatory disorders: immune therapies of type 1 diabetes: new opportunities based on the hygiene hypothesis. *Clin Exp Immunol* 2010;160(1):106–12.
- [17] López-Isac E, Martín J-E, Assassi S, Simeón CP, Carreira P, Ortego-Centeno N, et al. Brief Report: IRF4 Newly Identified as a Common Susceptibility Locus for Systemic Sclerosis and Rheumatoid Arthritis in a Cross-Disease Meta-Analysis of Genome-Wide Association Studies. *Arthritis Rheumatol* (Hoboken, NJ) 2016;68(9):2338–44.
- [18] Okada Y, Mori M, Yamada R, Suzuki A, Kobayashi K, Kubo M, et al. SLC22A4 polymorphism and rheumatoid arthritis susceptibility: a replication study in a Japanese population and a metaanalysis. *J Rheumatol* 2008;35(9):1723–8.
- [19] Akhter E, Bilal S, Kiani A, Haque U. Prevalence of arthritis in India and Pakistan: a review. *Rheumatol Int* 2011;31(7):849–55.
- [20] Doenhoff MJ, El-Faham M, Liddell S, Fuller HR, Stanley RG, Schramm G, et al. Cross-Reactivity between *Schistosoma mansoni* Antigens and the Latex Allergen Hev b 7: Putative Implication of Cross-Reactive Carbohydrate Determinants (CCDs). *PLoS One* 2016 28;11(7):e0159542–e0159542.
- [21] Dieguez-Gonzalez R, Calaza M, Perez-Pampin E, AR de la S, Fernandez-Gutierrez B, Castañeda S, et al. Association of interferon regulatory factor 5 haplotypes, similar to that found in systemic lupus erythematosus, in a large subgroup of patients with rheumatoid arthritis. *Arthritis Rheum* 2008;58(5):1264–74.
- [22] Xu M-Q, Cao H-L, Wang W-Q, Wang S, Cao X-C, Yan F, et al. Fecal microbiota *Gastroenterol* 2015 7;21(1):102–11.
- [23] Maizels RM, McSorley HJ. Regulation of the host immune system by helminth parasites. *J Allergy Clin Immunol* 2016;138(3):666–75.
- [24] Rosendahl Huber SK, Camps MGM, Jacobi RHJ, Mouthaan J, van Dijken H, van Beek J, et al. Synthetic Long Peptide Influenza Vaccine Containing Conserved T and B Cell Epitopes Reduces Viral Load in Lungs of Mice and Ferrets. *PLoS One* 2015;10(6):e0127969–e0127969.
- [25] Rai DK, Segundo FD-S, Schafer E, Burrage TG, Rodriguez LL, de Los Santos T, et al. Novel 6xHis tagged foot-and-mouth disease virus vaccine bound to nanolipoprotein adjuvant via metal ions provides antigenic distinction and effective protective immunity. *Virology* 2016;495:136–47.
- [26] Rai M, Ingle AP, Gade AK, Duarte MCT, Duran N. Three Phoma spp. synthesised novel silver nanoparticles that possess excellent antimicrobial efficacy. *IET Nanobiotechnol* 2015;9(5):280–7.
- [27] Oliveira-Santos S, Motta-Franco J, Barreto I, Solé D, Gurgel R. Asthma in adolescents--Prevalence trends and associated factors in northeast Brazil. *Allergol Immunopathol (Madr)* 2015;43(5):429–35.
- [28] Oliveira SM de, Gomides APM, Mota LMH da, Lima CMBL, Rocha FAC. Intestinal parasites infection: protective effect in rheumatoid arthritis? *Rev Bras Reumatol* 2016; 5 pages.
- [29] Gorman JD, Lum RF, Chen JJ, Suarez-Almazor ME, Thomson G, Criswell LA. Impact of shared epitope genotype and ethnicity on erosive disease: a meta-analysis of 3,240 rheumatoid arthritis patients. *Arthritis Rheum* 2004;50(2):400–12.
- [30] Yamamoto K, Okada Y, Suzuki A, Kochi Y. Genetics of rheumatoid arthritis in Asia--present and future. *Nat Rev Rheumatol* 2015;11(6):375–9.
- [31] Burr ML, Naseem H, Hinks A, Eyre S, LJ G, Bowes J, et al. PADI4 genotype is not associated with rheumatoid arthritis in a large UK Caucasian population. *Ann Rheum Dis* 2010;69(4):666–70.
- [32] Ajendra J, Berbudi A, Hoerauf A, Hübner MP. Combination of worm antigen and proinsulin prevents type 1 diabetes in NOD mice after the onset of insulinitis. *Clin Immunol* 2016;164:119–22.
- [33] Rai J, Lok KI, Mok CY, Mann H, Noor M, Patel P, et al. Immunoinformatic evaluation of multiple epitope ensembles as vaccine candidates: *E coli* 536. *Bioinformatics* 2012;8(6):272–5.
- [34] Schütze T, Wilhelm B, Greiner N, Braun H, Peter F, Mörl M, et al. Probing the SELEX process with next-generation sequencing. *PLoS One* 2011;6(12):e29604–e29604.
- [35] Lagier J-C. Faecal microbiota transplantation: from practice to legislation before considering industrialization. *Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis* 2014;20(11):1112–8.
- [36] Cholapranee A, Ananthakrishnan AN. Environmental Hygiene and Risk of Inflammatory Bowel Diseases: A Systematic Review and Meta-analysis. *Inflamm Bowel Dis* 2016;22(9):2191–9.
- [37] Zhou S, Jin X, Chen X, Zhu J, Xu Z, Wang X, et al. Heat Shock Protein 60 in Eggs Specifically Induces Tregs and Reduces Liver Immunopathology in Mice with Schistosomiasis Japonica. *PLoS One* 2015 29;10(9):e0139133–e0139133.
- [38] Addo-Yobo EOD, Woodcock A, Allotey A, Baffoe-Bonnie B, Strachan D, Custovic A. Exercise-induced bronchospasm and atopy in Ghana: two surveys ten years apart. *Plos Med* 2007;4(2):e70–e70.
- [39] Amoah AS, Boakye DA, van Ree R, Yazdanbakhsh M. Parasitic worms and allergies in childhood: insights from population studies 2008-2013. *Pediatr Allergy Immunol Off Publ Eur Soc Pediatr Allergy Immunol* 2014;25(3):208–17. -live
- [40] de-Graft Aikins A, Unwin N, Agyemang C, Allotey P, Campbell C, Arhinful D. Tackling Africa's chronic disease burden: from the local to the global. *Global Health* 2010;6:5page.
- [41] Strachan DP, Ait-Khaled N, Foliaki S, Mallol J, Odhiambo J, Pearce N, et al. Siblings, asthma, rhinoconjunctivitis and eczema: a worldwide perspective from the International Study of Asthma and Allergies in Childhood. *Clin Exp Allergy J Br Soc Allergy Clin Immunol* 2015;45(1):126–36.
- [42] Hamid F, Wiria AE, Wammes LJ, Kaisar MM, Lell B, Ariawan I, et al. A longitudinal study of allergy and intestinal helminth infections in semi urban and rural areas of Flores, Indonesia (ImmunoSPIN Study). *BMC Infect Dis* 2011;11:83.

- [43] Bashi T, Shovman O, Fridkin M, Volkov A, Barshack I, Blank M, et al. Novel therapeutic compound tuftsin-phosphorylcholine attenuates collagen-induced arthritis. *Clin Exp Immunol* 2016;184(1):19–28.
- [44] López-Isac E, Martín J-E, Assassi S, Simeón CP, Carreira P, Ortego-Centeno N, et al. Brief Report: IRF4 Newly Identified as a Common Susceptibility Locus for Systemic Sclerosis and Rheumatoid Arthritis in a Cross-Disease Meta-Analysis of Genome-Wide Association Studies. *Arthritis Rheumatol (Hoboken, NJ)* 2016;68(9):2338–44.
- [45] Choi HH, Cho Y-S. Fecal Microbiota Transplantation: Current Applications, Effectiveness, and Future Perspectives. *Clin Endosc* 2016;49(3):257–65.
- [46] Hirota M, Murakami I, Ishikawa Y, Suzuki T, Sumida S, Ibaragi S, et al. Chemically Modified Interleukin-6 Aptamer Inhibits Development of Collagen-Induced Arthritis in Cynomolgus Monkeys. *Nucleic Acid Ther* 2016;26(1):10
- [47] Cayabyab MJ, Macovei L, Campos-Neto A. Current and novel approaches to vaccine development against tuberculosis. *Front Cell Infect Microbiol* 2012;2:154.
- [48] Frank R. The SPOT-synthesis technique. Synthetic peptide arrays on membrane supports--principles and applications. *J Immunol Methods* 2002;267(1):13–26.
- [49] Orenstein WA, Seib K, Graham-Rowe D, Berkley S. Contemporary vaccine challenges: improving global health one shot at a time. *Sci Transl Med* 2014;6(253):253ps11–253ps11.
- [50] Varier RU, Biltaji E, Smith KJ, Roberts MS, Jensen MK, LaFleur J, et al. Cost-effectiveness analysis of treatment strategies for initial *Clostridium difficile* infection. *Clin Microbiol Infect Off Publ Eur Soc Clin Microbiol Infect Dis* 2014;20(12):1343–51.
- [51] Johnson A, Song Q, Ko Ferrigno P, Bueno PR, Davis JJ. Sensitive affimer and antibody based impedimetric label-free assays for C-reactive protein. *Anal Chem* 2012;84(15):6553–60.
- [52] Liao X, Wang Z, Cao T, Tong C, Geng S, Gu Y, et al. Hypervariable antigenic region 1 of classical swine fever virus E2 protein impacts antibody neutralization. *Vaccine* 2016;34(33):3723–30.
- [53] Bangaru S, Nieuwsma T, Kose N, Thornburg NJ, Finn JA, Kaplan BS, et al. Recognition of influenza H3N2 variant virus by human neutralizing antibodies. *JCI Insight* 2016;1(10) pii: e86673
- [54] Elliott SE, Parchim NF, Kellems RE, Xia Y, Soffici AR, Daugherty PS. A pre-eclampsia-associated Epstein-Barr virus antibody cross-reacts with placental GPR50. *Clin Immunol* 2016;168:64–71.
- [55] Garin N, Koyanagi A, Chatterji S, Tyrovolas S, Olaya B, Leonardi M, et al. Global Multimorbidity Patterns: A Cross-Sectional, Population-Based, Multi-Country Study. *J Gerontol A Biol Sci Med Sci* 2016;71(2):205–14.
- [56] Puentes F, Dickhaut K, Hofstätter M, Pfeil J, Lauer U, Hamann A, et al. Immune Modulation and Prevention of Autoimmune Disease by Repeated Sequences from Parasites Linked to Self Antigens. *J Neuroimmune Pharmacol Off J Soc Neuroimmune Pharmacol* 2016; 11(4):749-762
- [57] Kundu P, Biswas R, Mukherjee S, Reinhard L, Dutta A, Mueller-Dieckmann J, et al. Structure-based Epitope Mapping of *Mycobacterium tuberculosis* Secretory Antigen MTC28. *J Biol Chem* 2016;291(27):13943–54.
- [58] Offermann LR, Schlachter CR, Perdue ML, Majorek KA, He JZ, Booth WT, et al. Structural, Functional, and Immunological Characterization of Profilin Panallergens Amb a 8, Art v 4, and Bet v 2. *J Biol Chem* 2016;291(30):15447–59.
- [59] Opuni KFM, Al-Majdoub M, Yefremova Y, El-Kased RF, Koy C, Glocker MO. Mass spectrometric epitope mapping. *Mass Spectrom Rev* 2016;
- [60] Rahman KS, Chowdhury EU, Sachse K, Kaltenboeck B. Inadequate Reference Datasets Biased toward Short Non-epitopes Confound B-cell Epitope Prediction. *J Biol Chem* 2016;291(28):14585–99.
- [61] Sakai Bizmark R, Kumamaru H, Nagata S. Reduced Asthma susceptibility from early childhood exposure to residing in developing country. *Pediatr Allergy Immunol Off Publ Eur Soc Pediatr Allergy Immunol* 2016;
- [62] Shi Y, Dong Y, Huang W, Zhu D, Mao H, Su P. Fecal Microbiota Transplantation for Ulcerative Colitis: A Systematic Review and Meta-Analysis. *PLoS One* 2016;11(6):e0157259–e0157259.
- [63] Burr ML, Naseem H, Hinks A, Eyre S, LJ G, Bowes J, et al. PADI4 genotype is not associated with rheumatoid arthritis in a large UK Caucasian population. *Ann Rheum Dis* 2010 Apr;69(4):666–70.
- [64] Addo-Yobo EOD, Woodcock A, Allotey A, Baffoe-Bonnie B, Strachan D, Custovic A. Exercise-induced bronchospasm and atopy in Ghana: two surveys ten years apart. *Plos Med* 2007;4(2):e70–e70.
- [65] Yamamoto K, Okada Y, Suzuki A, Kochi Y. Genetics of rheumatoid arthritis in Asia--present and future. *Nat Rev Rheumatol* 2015;11(6):375–9.
- [66] Sieberts SK, Zhu F, García-García J, Stahl E, Pratap A, Pandey G, et al. Crowdsourced assessment of common genetic contribution to predicting anti-TNF treatment response in rheumatoid arthritis. *Nat Commun* 2016;7:12460.
- [67] Yarwood A, Viatte S, Okada Y, Plenge R, Yamamoto K, Barton A, et al. Loci associated with N-glycosylation of human IgG are not associated with rheumatoid arthritis: a Mendelian randomisation study. *Ann Rheum Dis* 2016;75(1):317–20.