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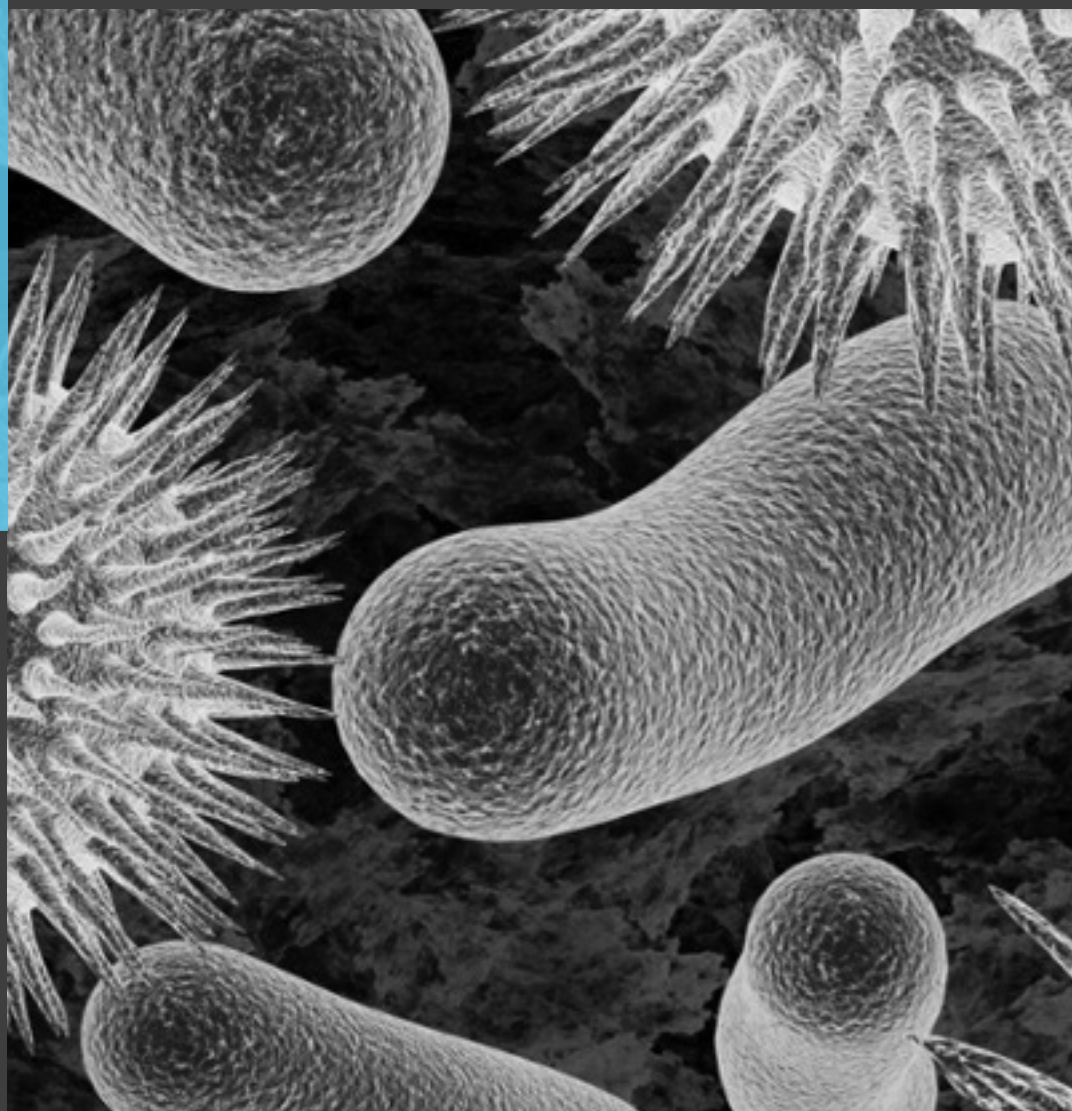
MICROBIOTA
A FOREIGN RECRUIT FOR DEFENCE

BECAUSE, OUR GENOME MIGHT NOT BE ENOUGH TO FIGHT THE UPCOMING BATTLES



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ABSTRACT

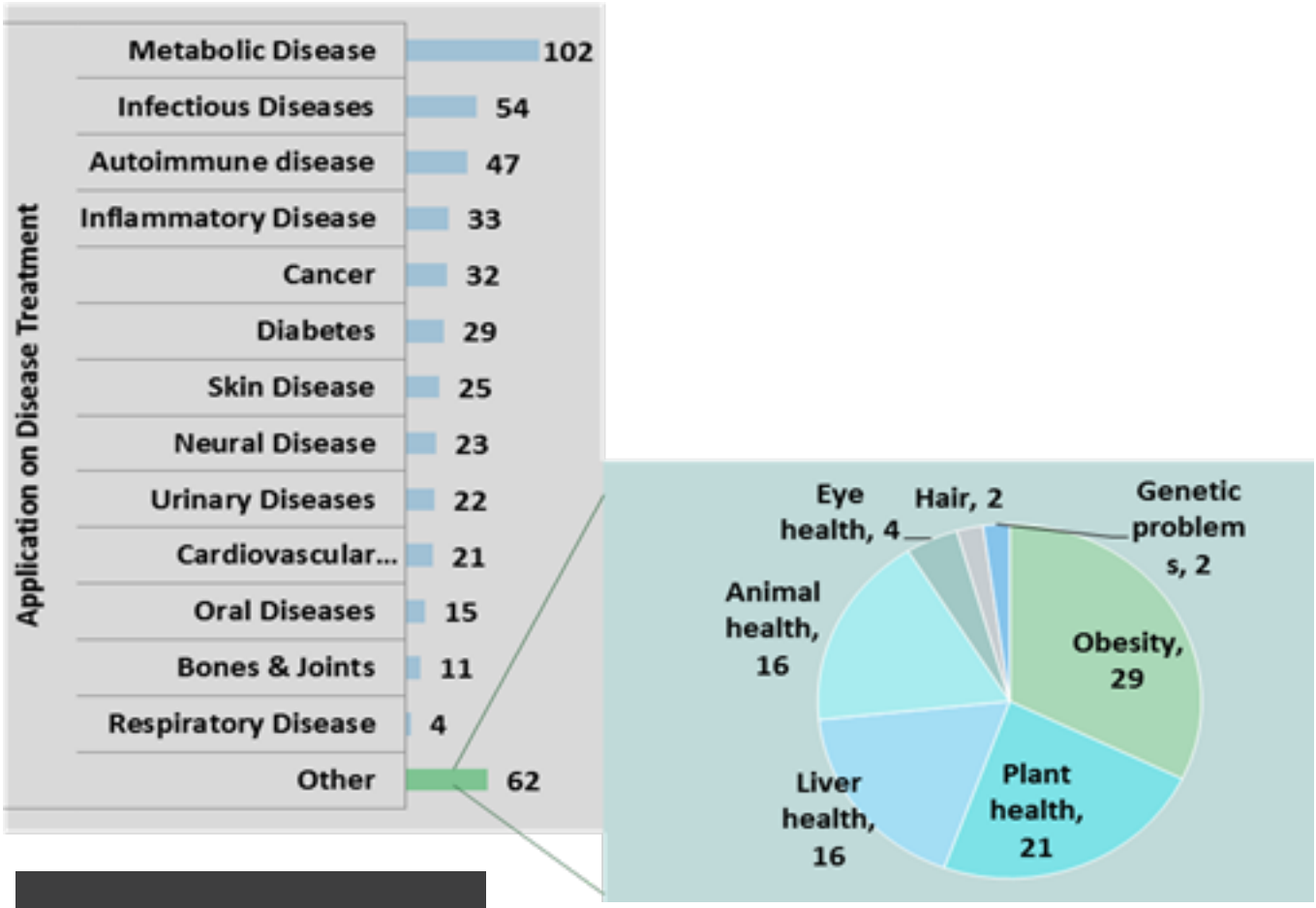
Microbes have always been seen in a negative light and as foreign particles invading our host system. Mostly it has been true considering virus and its activities, but not all of them have been bad guys. Some of them live in our gastrointestinal tract and fight against severe disease causing pathogens. Studies have showed that gut microbial transplant from healthy patients to dysbiotic guts have reduced the suffering of latter. This not only proves that gut microbiota beneficial but also paves a path towards customized medicines based on individual's gut condition. Identification of beneficial microbes, culturing them and then performing transplantation would not only increase immunity and resistance but would also prevent the disease before its happening.

CONTENTS

INTRODUCTION

Our Better Halves

Microorganisms are found everywhere and even in places invisible to naked eye. Discovery of DNA sequencing made it easier to track down and study bacteria and other organisms that could not be cultured. Apart from studying microorganisms, the first revelation that bioengineering techniques brought to this scientific era was the presence of diverse and large communities inside living organism's guts, skin and on every surface available. Microorganisms got classified on the basis of nutrition they prefer, environment that they wish to survive and that included type of hosts they wanted to survive into. Though not all relationships proved to be symbiotic but many did and it made easier for researchers to study the better halves.

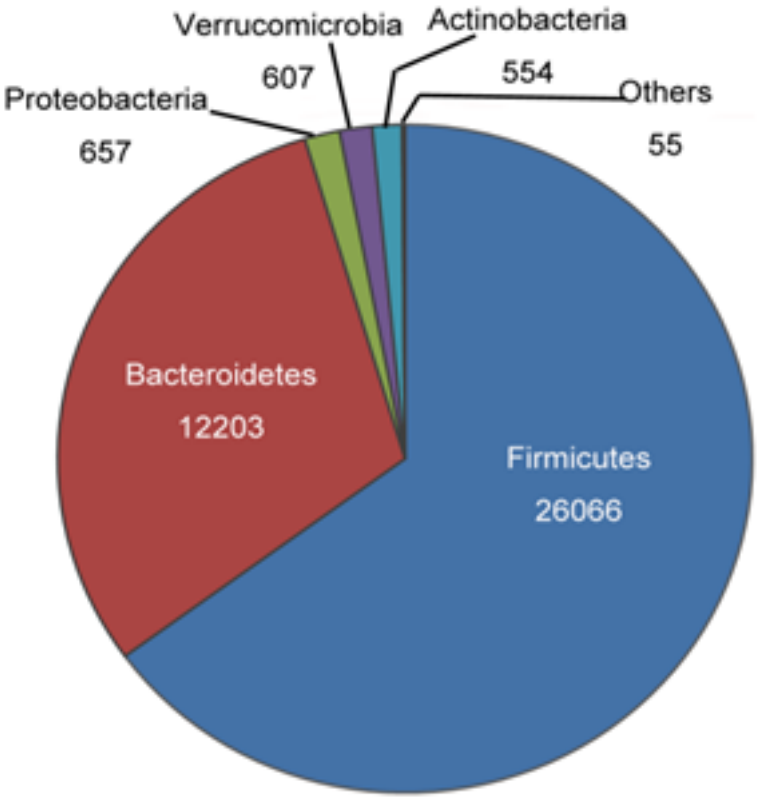


Maximum number of patents were inclined towards treating metabolic disease using microbiome therapy. As per the study, in metabolic diseases major focus was on Gastro intestinal disorders, irritable bowel syndrome, colitis, diarrhea, crohn's disease and intestinal dysbiosis. Other disease category includes Obesity, plant health, liver health and animal health. Plant health includes crop resistance, improving beneficial traits, improved tolerance, soil cementation and restoration and plant growth. Animal health includes factors such as enhanced livestock livability, increased milk yield, animal productivity, improved meat flavor, improved disease resistance.

It is preferred to call microbiome, specifically gut microbiome as better half as there are numerous functions carried out by these microorganisms which are important for our survival. Unaware of this, we have underestimated their presence in our system for long. Their work at molecular level has now instigated scientist to study its effect on host in both healthy and diseased state. Once understood how they affect our lives, manipulation of gut microbiota isn't far behind for the betterment of human lives.

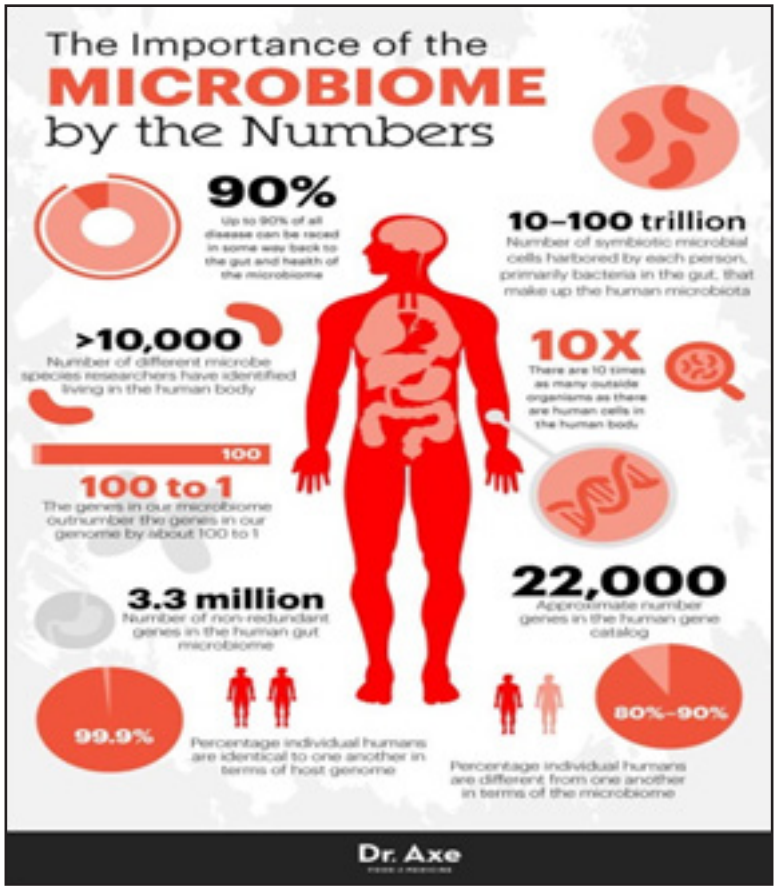
An ecological network of microbial community inhabiting in a particular system, with unique physio-chemical properties is called a microbiome. This term is not only limited to define microorganisms living together but it also encapsulates their various mechanisms along with their behaviour to external environment and to each other. Previously the term was misinterpreted as the collection of total microbial genome present in their inhabiting system. So, microbiota formed the microorganisms living in a microbiome.

Human microbiome and its effect



Source: https://www.researchgate.net/figure/26326168_fig12_Figure-4-Gut-bacteria-compositionThe-pie-chart-shows-the-distribution-of-gut-bacteria

Once Human genome project made news for successful its sequencing. Now it is the turn of an overlapping project to make same kind of news and generate same curiosity in bioengineering world. The Common Fund's Human Microbiome project (HMP) is on its way to develop research to ensure study of microbes that live in our bodies and benefit to our health. For every one gene present in our genome there are hundred genes of microbiome related and linked to it. Researchers claim that one third of metabolites found in our circulatory system are that produced by gut microbiota. Thus, the changes or manipulations if ever done to one's microbiota would change host's immunity and cellular activity and could also lead to new discoveries in therapeutics.



Source: https://www.pinterest.com/mslstar/mind-gut-microbiome-microbiota-probiotics-prebioti/

EFFECT ON HEALTH CONDITIONS

1. Research has indicated that gut microbiome plays vital role in maintaining our immune system. Every diseased condition that has an inference till now has a column written about the gut condition and its microbiome during the phase of infection. So, it implies that gut microbiome somewhere is responsible for protecting host against foreign invasion. Its implications came into light when faecal transplants made their way to medical news. This

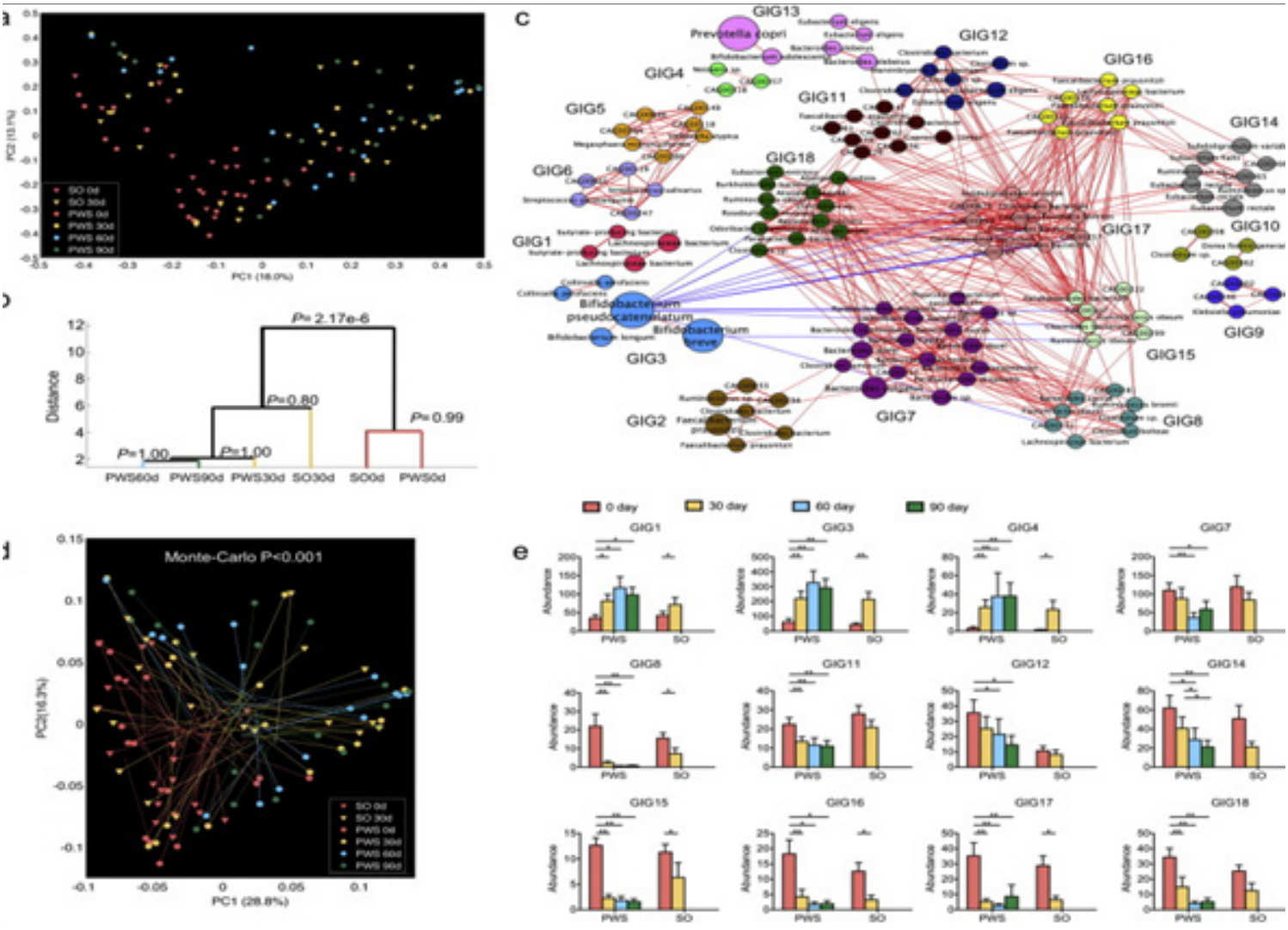
was done to patients suffering from ***Clostridium difficile infection (CDI)***. They had multiple recurrences of CDI. With no alternative left in hand as it was becoming difficult to treat them with existing antibiotics, they were suggested with faecal transplant.

Source: https://arstechnica.com/science/2016/05/the-white-house-announces-121-million-microbiome-initiative/

With increase in number of patients suffering from different diseases that could be cured by altering the gut microbiome, White House in May 2016 announced 'National Microbiome Initiative' with a budget of more than $500 million for the study and use of microbiome.

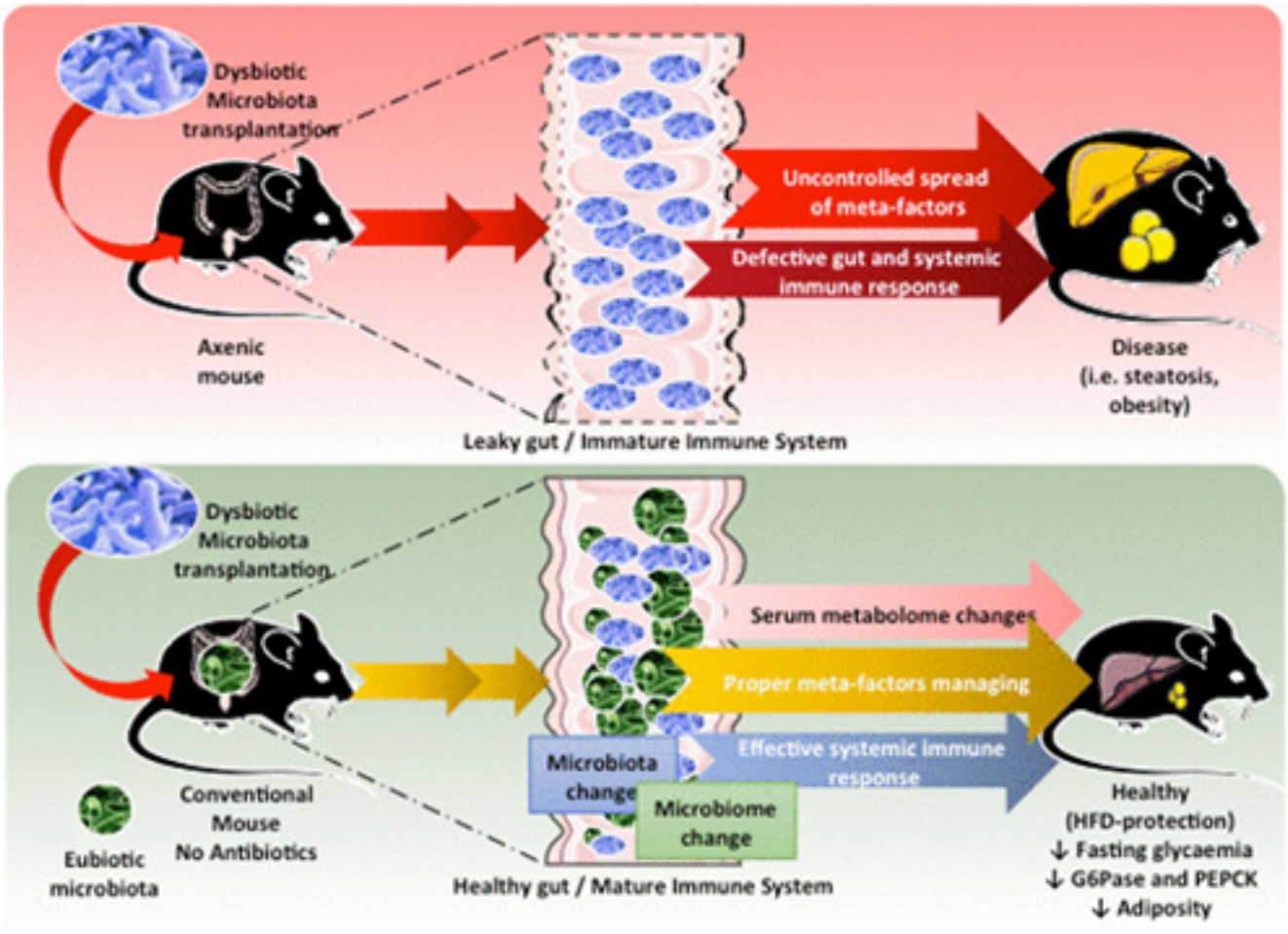
2. The colonization of gut microbiome begins after birth. It is a critical process as it dependent on nutrition of the new born. Among several reasons that human milk is considered better for feeding the new born than artificial or cow's milk is it's being an important factor in initiation, development and composition of gut flora. Composition of human milk like lactic acid bacteria (lactobacilli) and bifidobacteria are important for infant health and also provide source of microorganisms.

3. Not only in infants but gut microbiome plays a crucial role in maintenance of diet related obesity. Children having improper diet or suffering from genetic mutations are usually victims of obesity related diseases. Our lack of information about cause and effect of disease leads to slow and retarded treatment. Obesity can be of many types but research was mostly done on Prader-Willi syndrome (PWS genetic obesity) and it was found that the children suffering from PWS shared similar dysbiosis in their gut microbiota with those patients having diet related obesity.



Source: http://www.sciencedirect.com/science/article/pii/S2352396415300645

Gut microbiota from obese patients was transplanted into germfree mouse and an increase in fat deposits was seen in recipients. Using broad range antibiotics helped in reduction of dysbiotic gut microbiota. Same result was recorded when gut microbiota of healthy patients was transplanted into effected mouse. It increased its insulin resistance in a similar manner done by broad range spectrum. So, it was suggested that diet with non-digestible and fermented carbohydrates would result in beneficial groups of bacteria i.e. bifidobacteria and reduced endotoxin producers that would reduce the suffering if not remove it. It is certain that gut microbiota dysbiosis is responsible for many systemic disorders, metabolic diseases and impaired liver function.



Source: http://msb.embopress.org/content/13/3/921

PROPOSED SOLUTION

'Prevention is better than cure'. This statement has been underestimated in our health industry for too long, but recently there has been a wakeup call for the same. Precision medicine has made its way to our biological world and it will be just a matter of time, when fighting against diseases would be as easy as a sneeze. It is one of the examples set for customization tool box, where an account of individual gene variations, environment and lifestyle is taken into consideration.

One of such considerations is microbiota which plays key role in response to a treatment. This approach is based on the understanding of how microbiota is responsible and functional in each disease. One of the main reasons why it has not been included, this approach in market is lack of good clinical trials. The prototype for research has been described but additional work to illustrate successful implementation is still pending.

These are the steps that are to be followed during designing a precision medicine on basis of individual's microbiota:

1. Microbiota composition and function
2. Microbiota assessment
3. Identification of deleterious organisms
4. Identification of deficient microbiota functions
5. Microbiota modulations
6. Customized therapy

Now to perform these steps different approaches can to be followed:

1. **Gene circuits:** These are constructed using libraries of genetic parts so that microbial production is enabled from therapeutic proteins. Introductions of these produced microorganisms into microbiota allow in-situ detection biomarkers along with drug production.

2. **Defining mixtures of microorganisms:** Community profiling is done for the clinical samples taken from healthy and infected patients respectively. Clinical isolates are then used for mixing microorganisms which can later be used to regenerate microbial system of an individual.

3. **Usage of Bacteriocins:** These antibiotic molecules are used to eliminate deleterious microorganisms and are thus selective in nature. So, their combination with engineered microbiota will provide enhanced therapeutic activity.

PIONEERS AT WORK

Though the market value of customized medicines may not have seen a big boost but over past few years many companies have invested in research and development related to gut microbiome.

1. **Rebiotix** is the first company that not only invested into research but also took it to a new level by bringing the microbiome based product as a drug to FDA. The drug designed by them is for prevention of recurrent CDI (Clostridium difficile infection) and is clinically advanced.

Rebiotix
Microbiota Restoration Therapy

Source: http://www.rebiotix.com/

2. **Seres Therapeutics** has also designed CDI prevention product with a solution based on usage of limited microbial mix that form spores.

3. **Second genome has established drug discovery platform** where they study the interaction of host genome and microbial genome inhabiting inside the host for the identification of new targets and drugs.

Source: http://allergiesandyourgut.com/tag/our-second-genome/

They have been working on:

i. **Inflammatory bowel disease:** It is responsible for severe inflammation in gastrointestinal tract. Through their research and development they have established a link between gut microbiome and opportunistic pathogens that take advantage of dysbiotic condition and promote conditions like ulcerative colitis and Crohn's disease.

ii. **Metabolic disease:** This again includes obesity along with type 2 diabetes. Transplant studies, as discussed earlier have suggested that there are specific microbes which on introduction into host system result in weight gain or loss. Thus leading to obesity or reverse.

iii. **INFAT:** Another product of its kind has been launched into market claiming to be closest source to human breast milk. It is a joint venture of AAK and Enzymotec: Advanced lipids.

Source: http://www.mar-comit.com/case-studies/case-study-infat

Its formulation supports colonization of lactobacilli and bifidobacteria in infants. Both of these cultures are beneficial gut microbes and help fight infections in first stage of life. The clinical study stated that INFAT might affect intestinal microbiota during first week of birth.

CONCLUSION

1. Initiative taken towards research of gut microbiota has given opportunity to cure disease before it could spread and become a mess.

2. First step towards healthy gut microbiota is proper nutrition specific to an individual's profile. Apart from brands seeking research and therapeutics in these fields, there are also companies that are interested in counselling people on their nutrition; thus, providing society with personalized nutrition therapy and precision medicine therapy.

3. Development of easy screening techniques and making microbial markers readily available is now on rapid progress, as benefits of healthy gut microbiome are in light.

Every useful technique has its limitation so does precision medicine:

1. Consequences of changing microbiota environment: For we have hypothesized that using correct mixture would result into desired effect, but, what else might get changed by altering the composition is yet to be tested and clarified.

2. Something like graft rejection: It is difficult to say anything about the survival of engineered microbiota in a new environment and vice-versa. Our immune system is very selective towards foreign components specifically microorganisms. So, this may be treated as one of the major challenges for engineered microbiota.

3. Transmission of engineered microbiota: This should be restricted as it may or may not prove fatal to other individual. So modified microorganisms must not show transmission activity

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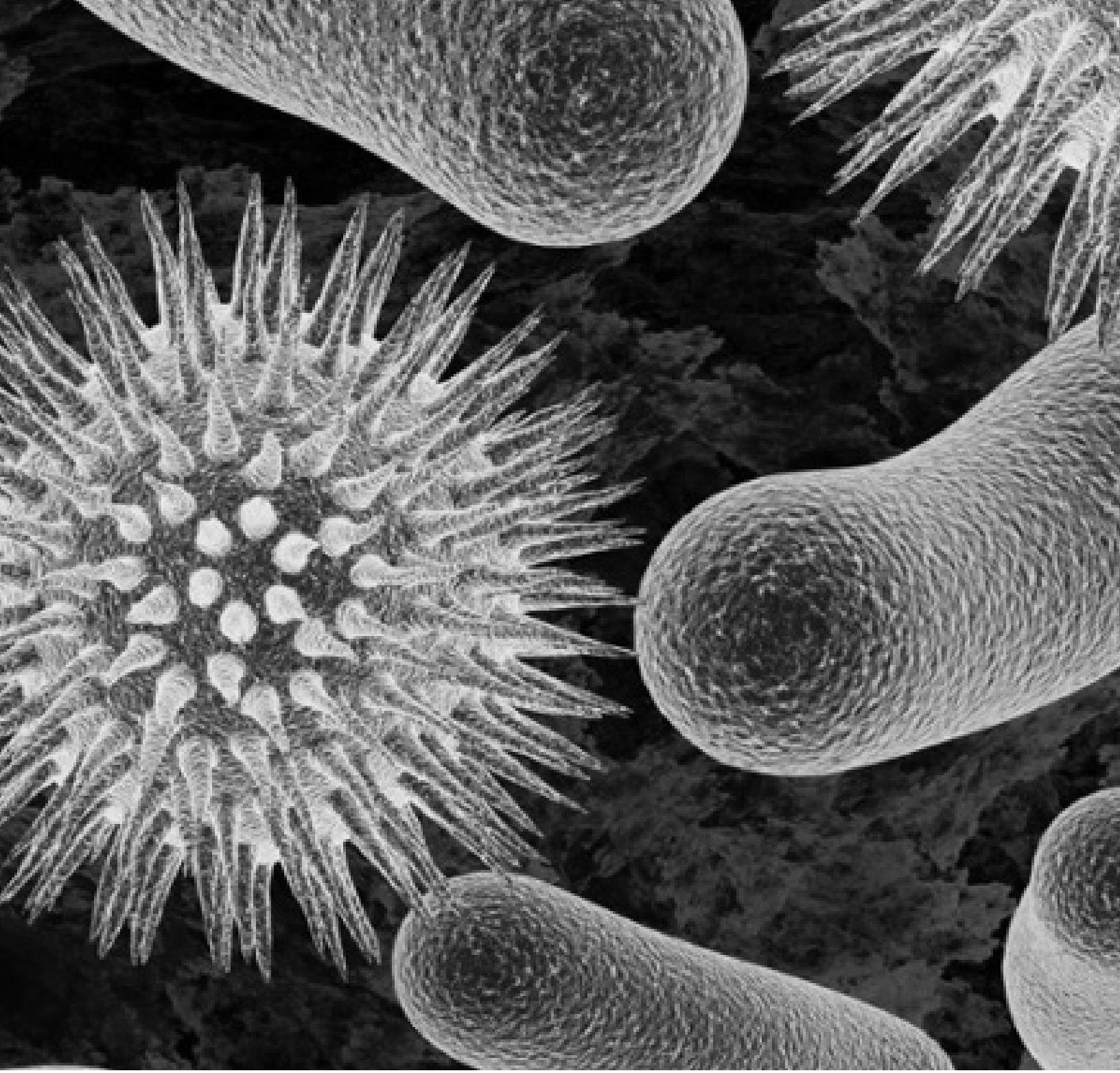

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