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3 ADM Expands Health & Wellness Capabilities With Agreement to Acquire Probiotics International Limited

Archer Daniels Midland Company (NYSE: ADM) announced that it has reached an agreement to acquire Probiotics International Limited (PIL), a U.K.-based provider of probiotic supplements for human, pet, and production-animal use. The all-cash transaction will be valued at £185 million, subject to customary adjustments.

PIL, based in Somerset, U.K. — and known under its umbrella brand Protexin — is a leading provider of probiotic supplements for human wellness and animal markets, including aquaculture, equine, livestock and companion animals. With sales into more than 60 countries, PIL produces the popular Bio-Kult brand of probiotic supplements along with contract-manufactured products. The company has about 160 employees.

Protexin Healthcare is dedicated to producing innovative, research based probiotic products of the highest quality for the healthcare market. The natural supplements they manufacture are extensively researched for safety and efficacy. Protexin works closely with leading universities and research centres around the world on a range of on-going research programmes. Every product produced by Protexin is manufactured in their own purpose built, state-of-the-art facility in Somerset, U.K. All products are subject to the same high standard of production and quality control as

pharmaceutical products and they hold the following accreditations; cGMP (MHRA), ISO 9001:2008, FEMAS, VMD (category 5), each of which involves regular audits to ensure standards are maintained.

Protexin has also been awarded The Queen's Award for Enterprise in International Trade in both 2011 and 2016 as well as a 2* Best Company to work for in 2018.

4 MaaT Pharma Presents Positive Phase 1b/2a Study Results in Acute Myeloid Leukemia Patients

MaaT Pharma announced the results from its ODYSSEE (NCT02928523) Phase 1b/2a clinical trial demonstrating that the Company's proprietary MaaT Microbiome Restoration Biotherapeutic (MMRB) therapeutic is able to restore a functional microbiome in acute myeloid leukemia (AML) patients after having undergone intensive chemotherapy and multiple courses of antibiotics.

The study was designed to investigate the safety and feasibility of reestablishing a functional microbiome using MaaT Pharma's therapeutic as well as evaluating initial signs of efficacy including reduction of intestinal inflammation and the control of detrimental antibiotic-resistant bacteria. Due to the harsh treatment regimens, AML patients lose their functional microbiome and experience a variety of severe complications that dramatically impact outcomes and quality of life. MaaT Pharma's MMRB therapeutic aims to restore microbiome function and improve clinical outcomes in these patients. The data were presented at 6:15 pm Pacific Time on December 1st, 2018 at the 60th American Society of Hematology (ASH) Annual Meeting and Exposition held in San Diego, California.

In total 25 AML patients were treated in the clinical trial. At the time of admission, fecal microbiota was collected from each patient, conditioned, processed and frozen according to GMP conditions. Following the first round of chemotherapy and antibiotic treatment, patients were administered two doses of the collected fecal microbiota as an enema 24 hours apart after hematopoietic recovery and before undergoing the second round of chemotherapy. Blood and fecal samples were collected on three separate days, (1) on day 0, at the time of patient inclusion in the trial, (2) on day 29, following hematopoietic recovery after the first round of intensive treatments and (3) on day 40, before the start of the consolidation chemotherapy. Microbiome profile evolution was analyzed using high-resolution metagenome sequencing and patient follow-up was scheduled for 6 months and 12 months after inclusion.

Overall, reintroduction of the

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patient's own gut microbiome through MaaT Pharma's proprietary process was well tolerated and no severe adverse events were reported. Metagenomic analysis of the patient samples collected on days 0, 29 and 40 using MaaT Pharma's proprietary big data analysis platform, GutPrint® showed that the MMRB therapeutic restored significantly greater than 90% of the microbial species diversity and structure at day 40, ten days after treatment, including a 43% reduction of the overall expression of antibiotic resistance genes. Most importantly, gut inflammation was significantly reduced to near-baseline levels following MMRB treatment as measured by fecal neopterin biomarker. These results also correlated with the significant reduction of pro-inflammatory bacterial families and restoration of beneficial species among the Lachnospiraceae and Ruminococcaceae families.

5 BIOASTER, Bio-Rad and Genetic Analysis Collaborate to Develop Novel Microbiome-Based Diagnostics for Metabolic Disorders

BIOASTER, the French Technology Research Institute for Microbiology and Infectious Diseases, announced the initiation of a collaborative program with BIOASTER, Bio- Rad Laboratories, Inc. and Genetic Analysis aimed at evaluating microbial dysbiosis signatures in the field of metabolic disorders.

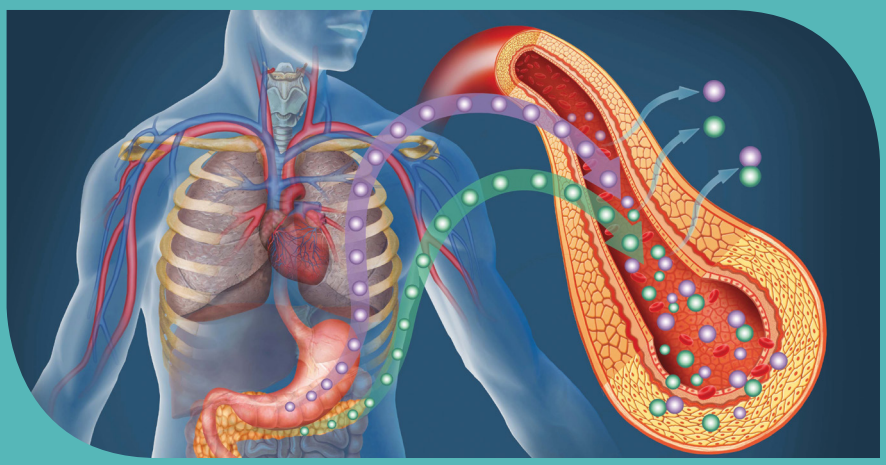
This project is a unique opportunity for BIOASTER to capitalize on its breakthrough deep and 16S-targeted sequencing technologies and advanced pipelines of data analysis for highlighting new gut microbiome biomarkers of medical added value. Endocrine and metabolic diseases are among the most common contemporary human afflictions in western countries and particularly in the United States. The high prevalence and incidence of common metabolic disorders such as diabetes and obesity have been confirmed through large population-based studies. Moreover, an increasing number of studies show that deregulation of gut microbiota composition ('dysbiosis") is associated with onset of metabolic diseases and may impact treatment.

This original collaboration between Bio-Rad, a world leading provider of life science research and clinical diagnostic products, Genetic Analysis, a Norwegian company renowned in microbiome molecular diagnostics and BIOASTER will add an innovative edge of this research program by examining gut microbiota signatures for diagnostics. Genetic Analysis and Bio-Rad previously announced in December 2017 a supply and distribution agreement for Genetic Analysis's GA-map® clinical test for gut dysbiosis.

6 Enterome Signs Global Licensing, Co-development and Co-promotion Agreement with Takeda for the Treatment of Crohn's Disease

ENTEROME SA, a clinical-stage biotech company developing innovative therapies to treat microbiome-associated diseases with a focus on auto-immune disease and cancer, has entered into a global licensing, co-development and co-promotion agreement with Takeda Pharmaceutical Company Limited ('Takeda"). The agreement covers Enterome's lead investigational drug candidate EB8018 in patients with Crohn's disease, with the potential to expand to other gastrointestinal (GI) disorders and liver diseases.

Enterome will receive an upfront payment of $50 million and commitment from Takeda to make



Human Microbiome: A GLOBAL OVERVIEW OF CLINICAL TRIALS ACTIVITY

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While "healthy" microbiome remains to be defined, microbiome disruption is associated with numerous diseases, offering new therapeutic opportunities if causalities are demonstrated. Europe is at the forefront of the understanding of the microbiome and is well placed to play a major role in the future, be it for nutrition or pharmaceutical applications.

Among the ~2,100 microbiome clinical trials listed on the clinicaltrials.gov global database from 2000 to 2017, 35% of the studies are conducted in Europe, followed by 33% in the USA. China is third with only 5% of the overall number of studies. Nonetheless, the number of Chinese clinical studies is thought to be underestimated. Indeed, after merging the previous database with the Chinese Clinical Trials Registry, the number of Chinese microbiome clinical studies is twice higher representing about 10% of the overall microbiome studies.

Europe was responsible for the initiative of the first trial mentioning microbiome in 2000, while the USA tackled the subject in 2006 and China in 2009. Moreover, Europe represents 32% of the publications on the microbiome listed on PubMed from 2006 to 2017, versus 23% for the USA and 9% for China.

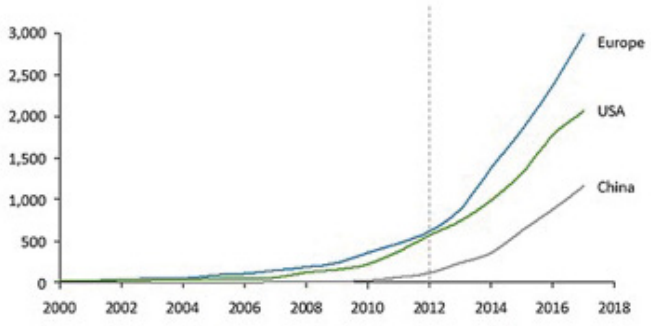

Fig 1: Number of publications on microbiome (PubMed)

Initially, microbiome therapeutic areas of interest have been gastrointestinal diseases (irritable bowel syndrome, inflammatory bowel disease, and Crohn's disease) and metabolic diseases (obesity and diabetes). They respectively represent 20% and 15% of the overall number of microbiome trials performed in Europe and the USA (2000-2017 period).

In recent years, the potential applications for microbiome have been extended to other therapeutic areas. Based on the number of clinical trials (Clinicaltrials.gov), the therapeutic areas that progress the fastest are central nervous system diseases, infectious diseases and oncology. The number of clinical trials in oncology, including a microbiome analysis, is growing at a fast pace in Europe with +41% p.a. since 2011, but it is still behind the USA in volume. Indeed, microbiome trials in oncology already represent 7% of the overall number of trials conducted since 2000 in the USA while it represents just 2% in Europe.

The first microbiome-based therapeutic treatments are already emerging, such as the fecal microbiota transplantation (FMT). Most of the interventions consist of introducing the microbiota from a healthy donor into a patient. The FMT is successfully used to treat Clostridium difficile infections (CDI) but it could also be applied to counteract gut dysbiosis following heavy treatments like chemotherapy. For instance, Maat Pharma, OpenBiome, or Rebiotix are biotechs developing FMT solutions. It requires the access to a biobank with characterized feces from healthy donors. However, the legislation around FMT is still to be defined. In the USA, it is classified as a biologic product and a drug only for CDI. In Canada, it is registered as a new biologic drug and its use is restricted to clinical trial. There is no regulation at the European level, up to date the countries are setting their own rules. In France, it is considered to be a drug and aside from exceptional circumstances, FMT should only be administrated under a clinical trial. However, in the UK, the National Institute for Health and Care Excellence (NICE) allows the use of FMT in the NHS (National Health Service) for patients with recurrent CDI who are not responding to traditional therapies. With more clinical trials, regulations about FMT therapeutic solutions should be revisited in the future.

Besides the FMT, the pharma industry is also interested in other microbiome therapeutic solutions, such as the 'phagotherapy', the antimicrobial peptides, and therapeutic adjuvant.

The interest of microbiome is not limited to the scope of the pharma industry. The food industry is actively contributing to the research on the microbiome. Indeed, the food industry holds a significant part in the emerging of microbiome clinical trials. Among the 15 clinical trials mentioning "microbiome" in Europe in 2008, 14 were related to the food industry. Moreover, 57% of European overall studies related to microbiome from 2000-17 come from the food industry. For the same period, in the USA the cumulated number of food microbiome trials represents 43% of the total. In both the USA and Europe, microbiome clinical trials related to the food industry accounts for about 50% of the studies in 2017.

The interest of the food industry in the microbiome relies mostly on the development of probiotics and prebiotics. Clinical trials investigate the role of different diets like the Western diet, Mediterranean diets, vegan diets, or gluten free diets on the microbiome. However, since the reinforcement of the European Food Safety Authority (EFSA) regulation on health claims in 2012, the number of food clinical studies is stagnating. Yet some Food companies such as PiLeJe are developing their products as a drug and therefore follow the same path as pharma companies with clinical studies to prove the efficiency and safety of their products.

Besides human health, another microbiome research area is emerging in the food industry, which is the food quality in the production plant. How to control the microbial ecosystems in food production to optimize sensory flavor of the products better? How to control spoilage bacteria? The researchers in the food industry need to better understand the relationship between shelf-life and microbial behavior. Advanced technologies such as the uses of phages or antimicrobial peptides (AMPs) are studied to target specific bacteria to prevent undesirable bacterial colonization (biopreservation).

Pharma and food industry interest in microbiome and human health is booming. Europe is at the forefront of human microbiome research, as it promotes the emergence of new biotech companies and developing microbiome-based products. However, human microbiome-related research activities and clinical trials take place in large volumes also in the USA and the rest of the world. The interest and engagement in the study and further understanding of human microbiome (and its clinical applications) is constantly increasing, both within the pharma and the food industry. In the future, pharma and food industries might cross-fertilize their microbiome discoveries and work together for standardization methodologies for a better understanding of microbiome ecosystems and functionalities.

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