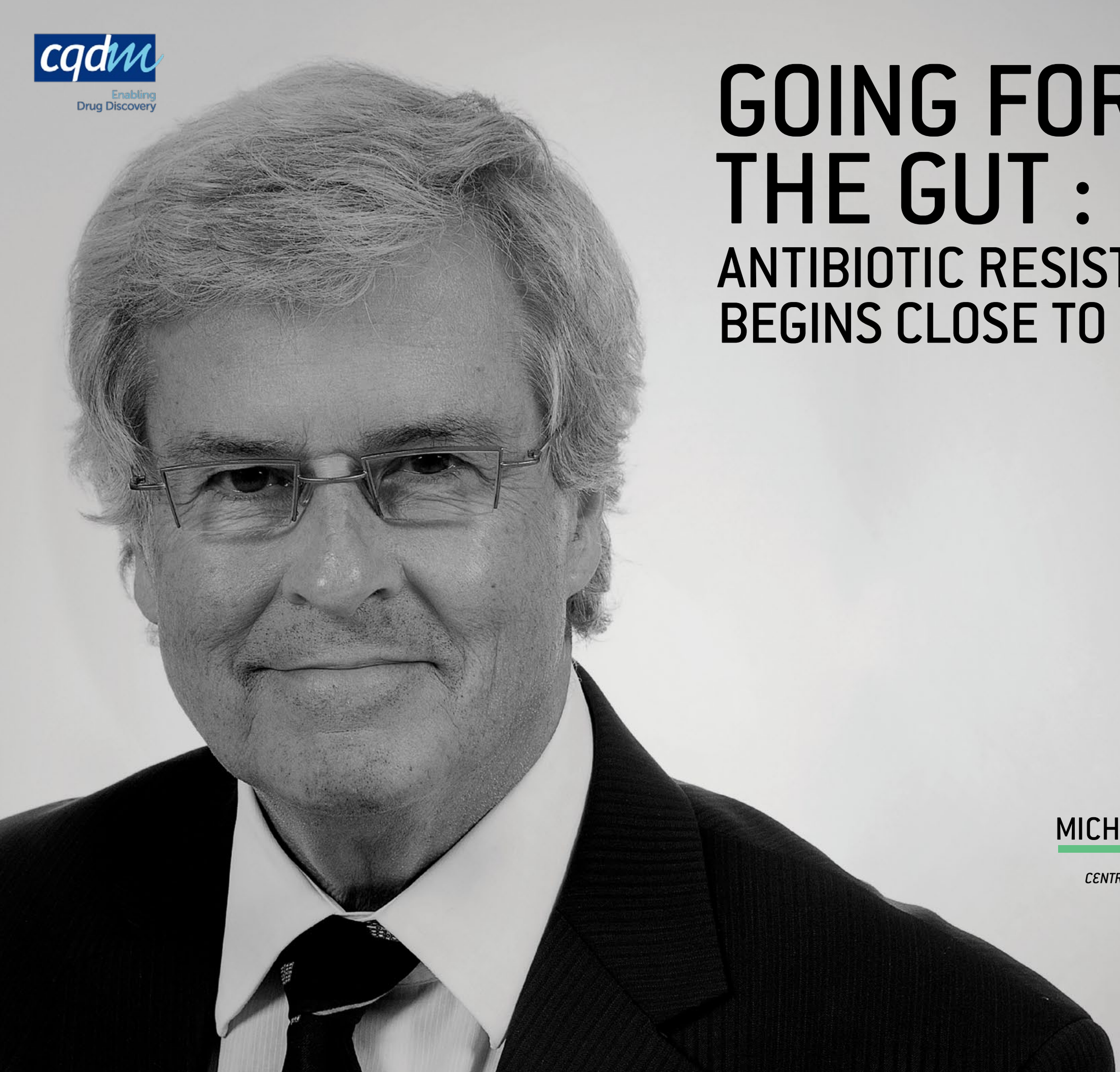
cqdm
Enabling
Drug Discovery

GOING FOR THE GUT :

ANTIBIOTIC RESISTANCE BEGINS CLOSE TO HOME



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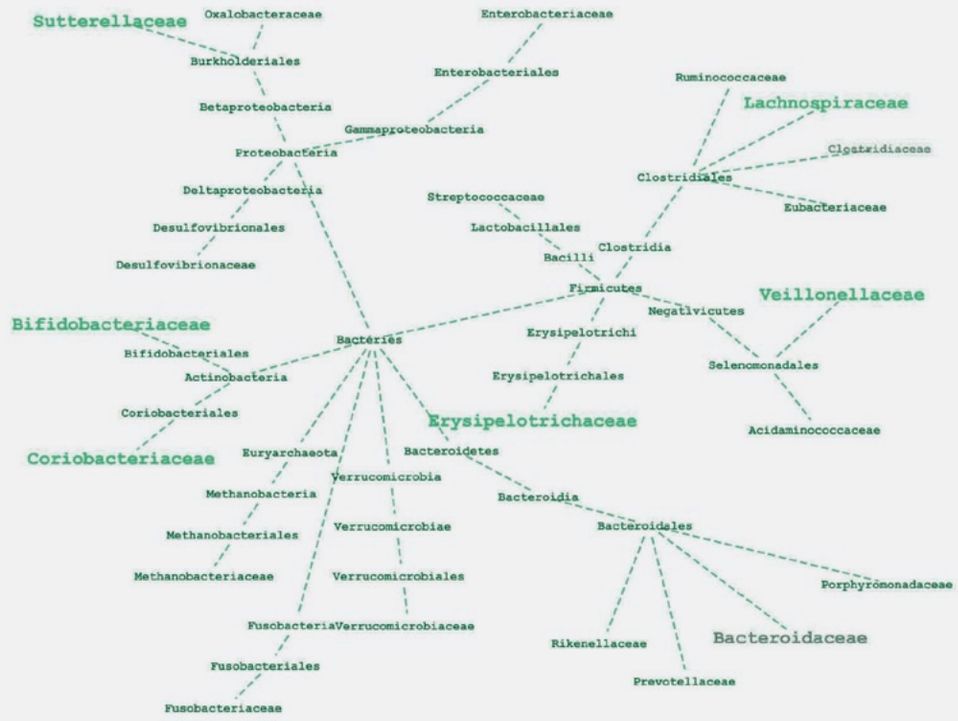
SELECTOMICS TO MONITOR AND PREDICT THE EMERGENCE OF RESISTANCE TO ANTIBIOTICS

FUNDING : $2M OVER 3 YEARS

IN THE SEARCH FOR CAUSES OF THE MAJOR PROBLEM OF BACTERIAL RESISTANCE TO ANTIBIOTIC DRUGS, LOOK NO FURTHER THAN YOUR OWN INTESTINAL TRACT. RESEARCHERS ARE EXPLORING THE COMPLEX MICROBIAL ECOSYSTEM OF THIS PART OF THE HUMAN BODY, WHICH COULD HARBOR MANY OF THE GENES THAT CAUSE ANTIMICROBIAL AGENTS TO LOSE THEIR EFFECTIVENESS. A BETTER UNDERSTANDING OF THIS PROCESS COULD POINT THE WAY TO TECHNIQUES FOR DEVELOPING NEW TYPES OF THESE IMPORTANT PHARMACEUTICAL COMPOUNDS.



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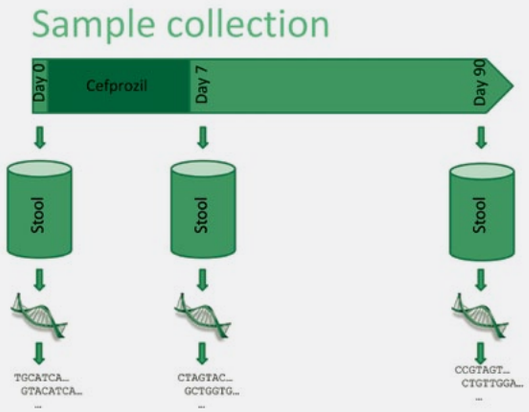
THE CHALLENGE

Antibiotics represent some of the most important drugs available to modern medicine, since they can often cure bacterial infections that would otherwise pose a serious health threat. Dozens of these potent molecules were identified during the 20th century, including such major products as penicillin and cephalosporin drugs. However, the cost and difficulty of discovering these agents have steadily increased, so that largest pharmaceutical firms are no longer actively engaged in this area. Concurrently, the bacteria targeted by existing agents have continued to evolve and have developed a resistance to several antibiotics. Compounded by virtually inexistent new-antibiotic output, these acquired resistances seriously limit our ability to effectively treat bacterial infections.



THE SOLUTION

Researchers at Université Laval are using selectomics as a strategy to address the challenges of monitoring and predicting the resistance of bacteria to antibiotics. This team posits that the human intestinal tract serves as a reservoir for resistance genes and is a key location where resistance genes can be selected and disseminated to pathogen species. By using the human microbiome to understand, predict and monitor the lateral transfer of antibiotic resistance, it should be possible to determine forms of antibiotic resistance which originate within our own bodies and the role of antibiotic pressure in promoting this emergence, laying the foundation for a new era of drug discovery. The selectomics strategy developed in this project will constitute useful tools to assess the potency of novel chemical compounds to select for resistance in order to develop effective infection-fighting products that are urgently needed.

MENTORS

Humphrey Gardner, AstraZeneca
Richard Korsmeyer, Pfizer
Terry Roemer, Merck

MAIN ACCOMPLISHMENTS

Since the beginning of the project in 2011, 40 participants have donated fecal samples that are representative of the microbiome of the human intestinal tract. After patient exposure to one of the widely used family of ß-lactam antibiotics, a program of high-throughput screening was performed to characterize the bacterial genes associated with resistance to these drugs. The result is an unprecedented database compiling more than 1,700 antibiotic resistance gene types for a total of more than 100,000 resistance gene sequences. This reference database, which will be made publicly available in 2015, has been largely automated to make for easier searching and expansion. The database helped analyze 72 human intestinal metagenome samples and 288 fecal bacterial cultures generated during the project. This dataset represents more than 1,593 billion nucleotides that were used to define the impact of antibacterial drug exposure on the composition of the human microbiota. In addition to this set of resistance-associated genes, a complete collection of cultivable resistant isolates from the selectome will be provided to CQDM's pharmaceutical members, together with all the appropriate documentation to perform the test and methods for suitable selectomics.

IMPACT

The socioeconomic impact of this project is considerable, as bacterial infections affect hundreds of millions people every year. Today, many of these infections do not respond to antibiotics. If the discovery of new antibiotics remains at a standstill, and resistance to existing antibiotics continues to reduce the number of effective drugs, our society could become vulnerable to a wide range of infections that will have no treatment or cure by the middle of the 21st century. By improving our understanding of how our own bodies enable bacteria to acquire drug resistance, this research introduces a tool that quickly identifies resistance genes that can compromise drug candidates. This capability should make the search for new antibiotics much more attractive by making it possible to minimize the prospect that bacteria could become resistant to these agents once patients begin to take them.

ROLE OF MENTORS

Although smaller biotechnology firms continue to explore the prospect of a few antibiotic compounds, the discovery of significant numbers of such drug candidates will accelerate much more rapidly with the participation of major pharmaceutical firms.

"We need the big ones to access the market," states principal investigator Michel G. Bergeron, who is optimistic that the interest these companies have expressed in selectomics can restore the lost momentum of antibiotic research by addressing the major problem of resistance. He adds that the mentors taking part in this project have been instrumental in helping researchers understand how their findings could be applied by the industry to predict resistance as new agents are being studied.

KEY FACTS

From the time of the first antibacterial approval in 1939 through the end of 2013, 155 antibacterial molecules have been used at some point in North America. Owing to the sequence of discoveries and withdrawals, this number peaked in 2000 where physicians could use up to 113 molecules to fight bacterial infections. By 2013 that number had dropped to 96, leading some observers to fear that within a few decades we will have no formal defense against the hundreds of bacterial pathogens that target human beings.