A Hi-Tech Cost-Effective BioFactory

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MRSB Sdn Bhd

(304399-W)

California, USA Selangor, Malaysia.

Macnalink Resources

- Macnalink Resources Sdn Bhd is registered in Malaysia, with corporate number 304399-W,

  Kuala Lumpur Malaysia
- MRSB is a biotech company

- Founders:
  - Ooi Boon Chong
  - Dr. Hwa A. Lim
  - + Others.

Expertise

- Business experience in Malaysia (B.C. Ooi)
- Biotech and biotech business management (H.A. Lim)

- Others (chemistry and molecular biology, etc).

Aim

- To establish a world class biotech company
  - in Malaysia, potentially with a window in US
  - to pursue a unique business opportunity
  - to capture domestic, ASEAN and overseas markets
  - by combining and tapping into

    - cutting-edge biotechnologies from the US with
    - resources native in and specific to Malaysia
    - provide employment and train local personnel.

Mission

- To develop a new genetic engineering system based on *Methylococcus* (a bacteria) which
  - can grow on methane or natural gas as sole source of carbon and energy
  - produce multiple valuable generic therapeutic and diagnostic proteins with the system
- Natural gas
  - is a much more cost-effective energy source than the organic nutrients
  - is rich in Malaysia
- Further supplemented by the low manpower cost in Malaysia, MRSB predicts a strong market position of MRSB products with competitive price.

Current Technology (Bottlenecks)

- Therapeutic, diagnostic and research proteins are produced in *E. coli*
- *E. coli* has historically become a real factory of many biomedical products
- But
  - The cost to produce one kilogram of proteins in *E. coli* >US$1,000,000
  - *E. coli* exists in human bodies and is potentially harmful to human.

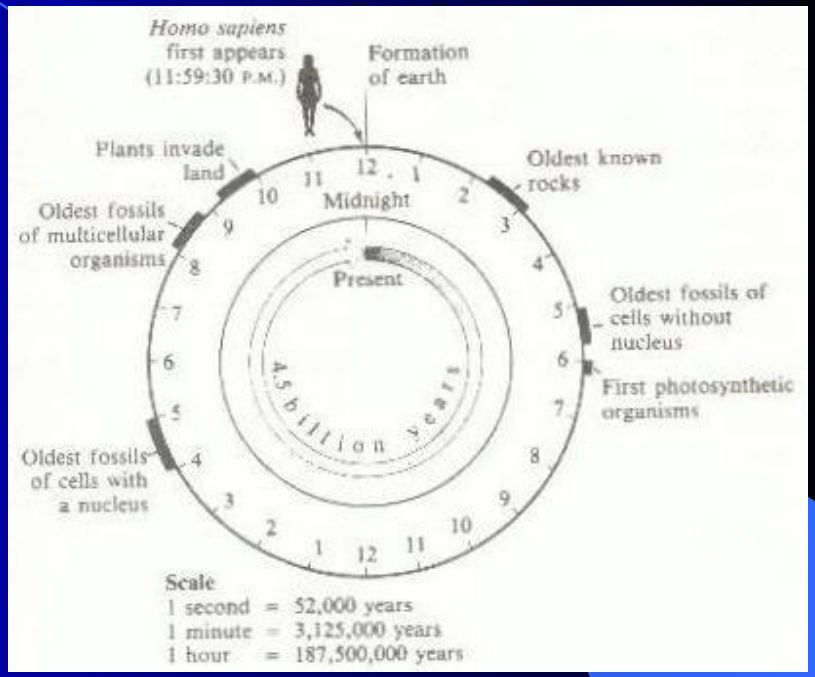
Value Proposition

- Vision:
  - Winners are whoever control economic ways to produce valuable proteins
- Proposition:
  - MRSB is proposing a
    - Innovative hi-tech
    - cost-effective
    - safe

    way to produce valuable proteins
- MRSB projects spin around the peripheral of one of the largest industries in Malaysia – bio- and natural resources.

Microbes

- Make up most of the earth's biomass
- Have evolved for some 3.8 billion years
- Have been found in almost every environment: heat, cold, radiation, pressure, salt, acidity, darkness, and where no other forms of life are found



- Less than 1% of the microbial have been described
- Most of them are not responsible for diseases
- Their diversity and range mean that they solved many problems that scientists are still seeking solutions
- Have been used in brewing, baking dairy and other industries.

- Normally scientists try to understand microbes by growing them in laboratory cultures
- But more than 99% of bacteria in the world cannot be grown in culture
- So their identities and environmental roles have remained unknown.

Methanotrophs

- Methanotrophs are ubiquitous bacteria that can use the greenhouse gas methane as a sole carbon and energy source for growth
- They thus play major roles in global carbon cycles, and in particular, substantially reducing emissions of biologically generated methane to the atmosphere

- *Methylococcus* is a methanotroph.

Methylococcus

- *Methylococcus* is a bacterial genus representing a group of bacteria that
  - can grow on methane or natural gas as a sole source of carbon and energy
  - does not rely on any organic growth factors
  - thrives in habitat temperature ranges from 30°C to 50°C



- These features have given *Methylococcus* a great potential to become a cost-efficient manufacturing factory to produce biologically and medically important proteins.

Methylococcus

- *Methylococcus* is not a bacterial species carried by human beings or any animals like *E. coli*
- In contrast, it broadly exists in tropical rice field, soil, methane seeps on the ocean floor, hot springs, and natural gas field at a high density (probably > 10,000 bacterial cells per gram of soil in Malaysia due to its high and right temperature for the *Methylococcus* bacteria)
- This feature means that *Methylococcus* will not cause any infections to human beings and to animals
  - whereas *E. coli* have been known to be a major cause of urinary tract infections, diarrheal diseases, even septicemia and meningitis in human.

Why Methanotrophs?

- Methanotrophs play an important role in the global energy cycle because they consume methane, a gas that is produced mostly by chemical processes in landfills, in the guts of ruminant livestock such as cows, and by oil and natural gas processing plants
- In recent years, environmental scientists have shown increasing interest in methanotrophs because their use of methane as a sole source of carbon and energy could possibly be harnessed to play an important role in efforts to reduce methane emissions that are generated by biological sources such as ruminants and landfills
- *Methylococcus* is a methanotroph.

Why Methylococcus?

- The organism's potential significance for biotechnology include the use of bacteriophage (viruses that infect bacteria) that have made a home in the genome
- Such phages could be exploited to genetically manipulate *Methylococcus* to more efficiently produce microbial protein for commercial animal feed, for example
- Intensive farming involves dealing with large numbers of animals, such as aquaculture
  - Imagine the process of having to vaccinate several thousand 10cm long smolt (young salmon):
    - have to catch the fish, while trying not to traumatize or damage them, and then individually inject each one with the vaccine
  - This process is very labor intensive, so it is easy to understand the attractiveness of the idea of an oral vaccine.

Why Methylococcus?

- Some bacteria species have already been "domesticated" to produce particular compounds such as insulin
- Researchers have been exploring how to exploit some of the unique characteristics of *Methylococcus* to develop novel vaccines that could be ingested rather than injected
- *Methylococcus* is a good vector or vehicle for transporting vaccine material orally because, unlike many other bacteria, it is not toxic. This is because its outer membrane does not contain any protein molecules that act as strong antigens (unlike some strains of *Escherichia coli*). This means that *Methylococcus* can be ingested harmlessly
  - If *Methylococcus* could then be modified to carry a viral coat protein, it could be used as an oral vaccine against that virus.

Why Methylococcus?



- Because of its unique characteristics, the bacteria *Methylococcus* has been attracting research interest since its discovery a couple of decades ago
  - As its name suggests, *Methylococcus* is a coccus, or roughly spherically shaped, encapsulated bacteria that is methanotrophic, or methane eating
  - Methanotropic bacteria can use simple organic materials, such as methane, the simplest of the hydrocarbons (CH_4), together with certain minerals to make the building blocks of life (simple sugars, amino acids and fatty acids)
  - Thus far, researchers have identified very few organisms capable of making these essential molecules. Most organisms, including humans, need to ingest these basic molecules in our diet or make them by breaking sown larger, more complex molecules
  - The idea of an organism that naturally contains the biological pathways to make these fundamental molecules is very interesting.

Why Methylococcus?

- The *Methylococcus* genome has been sequenced and the data is publicly available
  - The data has been released online since October 2004.

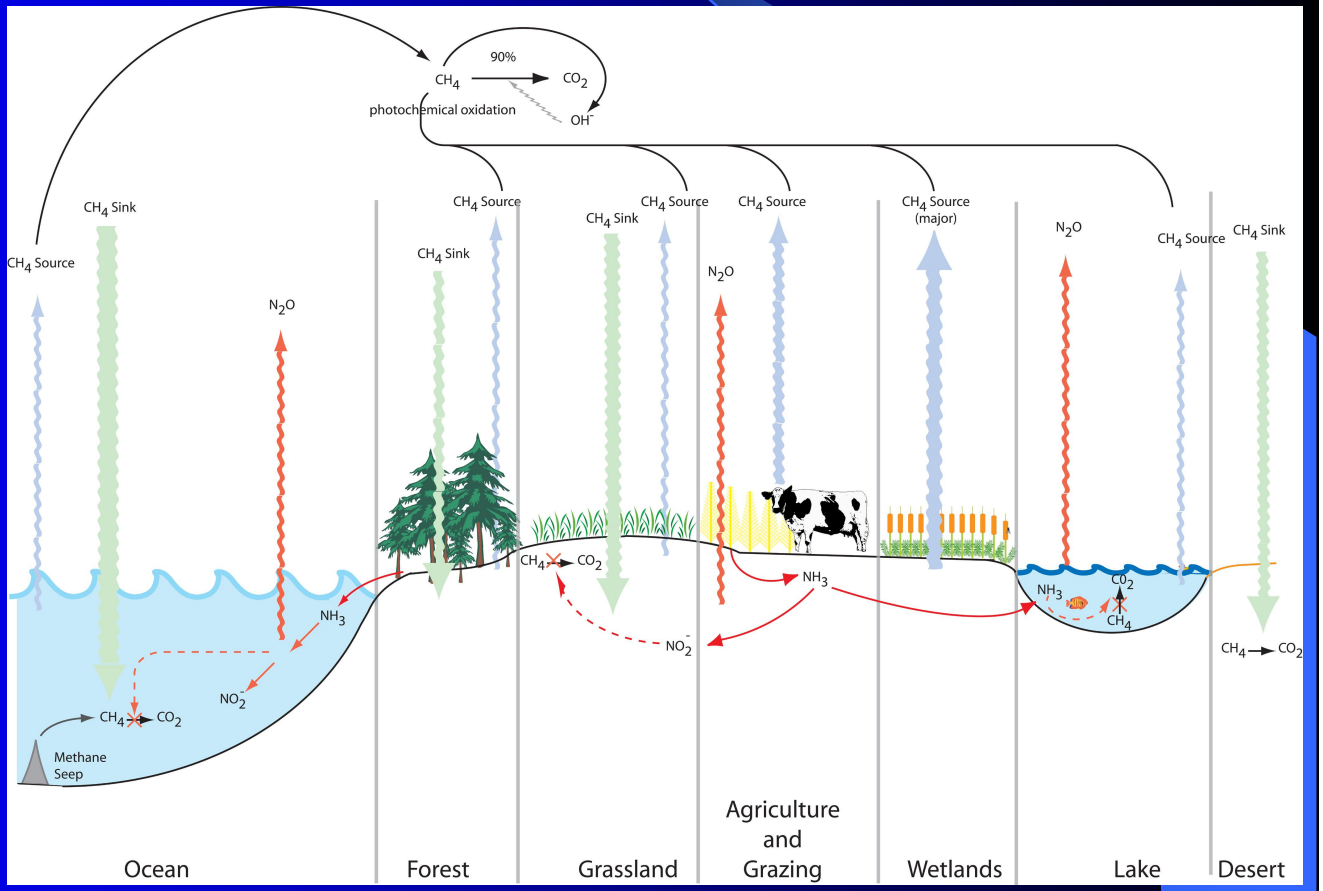
Complete genome size, bp	3,304,697
G + C percent	63.6
Total number of CDSs	3,120
Average CDS size, bp	962
Percent coding	90.9
Number of rRNA operons (16S-23S-5S)	2
Number of tRNA genes	46
Number of sRNA genes	3
Proteins similar to proteins of known function and role category	1,766
Proteins similar to proteins of known function but unknown role category (EUS)	109
Conserved hypothetical proteins	514
Hypothetical proteins	504

EUS, enzymes of unknown specificity.
DOI: 10.1371/journal.pbio.0020303.t001

General features of the *Methylococcus* genome

Why Methylococcus?

- *Methylococcus* is ubiquitous
  - Sea floor
  - Landfills
  - Padi fields
  - …



Future

- *Methylococcus* is just a beginning because of
  - all the advantages of working with this microorganism
  - resource consideration

- Later, MRSB will work with other microorganisms as well, including yet uncharacterized ones.

Methylococcus

- In addition to its potential to become a safe, cost-efficient manufacturing factory to produce biologically and medically important proteins
- The huge diversity of biological properties of *Methylococcus* bacteria has offered a high possibility of finding useful biological products by screening a *Methylococcus* bacterial library generated from diverse isolation sources
- A useful biological product can be a unique protein, an enzyme, or even an antibiotics.

Malaysia's Advantage

- Malaysia is one of the twelve mega biodiversity countries in the world
- At least 60% of the world's known species of flora and fauna are located in these mega biodiversity countries
- In Malaysia
  - ☑ The number of flowering plants is about 12,500 species;
  - ☑ 1,000 species of ferns and fern allies, many of which are unique and found nowhere else in the world;
  - ☑ Fungal species are expected to account for the bulk of the plant diversity, but at present an unknown number of species exist;
  - ☑ Fresh water swamps contain over 80 endemic species, with river systems hosting over 27 species;
  - ☑ The microorganisms present are poorly known as yet, with much study necessary to obtain comprehensive data.

Nature's Gift To Malaysia

- The microorganisms present in Malaysia are poorly known as yet, with much study necessary to obtain comprehensive data
- This is not only a problem in Malaysia, but it is a problem seen worldwide
- Bioprospecting, documenting and cataloging of Malaysian microorganisms and native species are a sure way of protecting the intellectual property of Malaysian heritage and natural endowments within Malaysia.

Malaysia's Gift To The World

- With Malaysia's rich biowealth, the potential is there
- So far the focus in biodiversity research has been on plant species
- It is high time for Malaysian scientists to also look at the fauna of the country's forest, particularly the microflora and microorganism population found in the soil, waterway and sea floor
- Biodiversity is Malaysia's inheritance and biotechnology is Malaysia's means to translate this great resource and endowment into wealth creation
- This is a golden opportunity that should not be missed.

MRSB
Piecemeal Technology

- MRSB will bring from USA the expertise in
  - building a *Methylococcus* bacterial library
  - establishing high throughput screening process for multiple biological products, including special binding proteins, enzymes, and antibiotics
- MRSB will apply recombinant DNA techniques to
  - construct gene-cloning and transferring tools for selected *Methylococcus* bacterial strains
  - eventually establish a manufacturing factory with *Methylococcus* for many valuable protein products.

MRSB's Innovativeness

- Old plus new biotechnology
  - Old, the natural capacity of *Methylococcus* as a biofactory
  - New, genetic engineering
- Genetic engineering is a mature technology
  - direct transfer from an advanced country
  - in fact, it is so routine that it is a part of molecular biology and has been practiced in Malaysia universities and research institutes
- *Methylococcus* is
  - abundant and native in Malaysia fields
  - strains are specific to different locations in Malaysia.

Market Segments

- Fine biomolecules
  - To identify 10 useful proteins or enzymes in 0-3 years
  - Each with sales of $10,000 - $100,000
- Tools for genetic engineering
- Antibiotics and other therapeutics
  - High value, high risk segment
  - each antibiotic ~ $100 million
  - Discover one within 0-2 years
- Contract services for screening
  - Biomolecule screening as short-term
  - Large scale production of biomedically valuable proteins as long-term
  - Profit margin ~100%, ~ 10 clients in year 2.

En Route To Market

- MRSB will spend two years to
  - construct multiple gene-cloning and transferring tools for *Methylococcus* bacterial strains
  - establish an intermediate scale fermentation facility
- With this system established, MRSB will be able to manufacture many valuable proteins at much lower cost
- MRSB's market value may be well positioned at above 100 million US dollars after the first five years of operation.

Work Plan

- Year 1
  - MRSB plans to identify ~ two useful biological products through screening the *Methylococcus* bacterial library MRSB has established
- Year 2 & 3
  - MRSB plans to identify four useful molecules in each following years
- Most of this type of products will be enzymes
  - Quick cash generators in early stage of MRSB piecemeal development.

Long-Term Plan

- Besides enzymes, MRSB will establish screening processes to seek
  - antibiotics and
  - anti-cancer therapeutics
- Risk:
  - Compared to enzymes, the probability of finding new antibiotics and anti-cancer therapeutics is much lower and the time spent will be much longer
- Opportunity:
  - However the chance is there and their market value is extremely high and therefore it is worth to pursue finding new antibiotics and anti-cancer therapeutics.

Off Ramp (Screening)

- The established screening processes for enzymes, antibiotics and anti-cancer drugs will be offered as service programs starting
  - in the second year to the universities, research institutes, technology parks, and other biotech companies primarily in Southeast Asian countries
  - later to biotech and pharma in advanced countries
- In the most unfortunate and worst case scenario of no useful products were found, the facility could be converted into a full screening contract service
- There is a trend to relocate contract services to cheaper labor nations, including Malaysia.

Intellectual Property Portfolio

- The products obtained through screening *Methylococcus* bacterial library and all of the gene-cloning and gene-transferring tools for *Methylococcus* bacterial strains will be internationally patented.

Safety Issues

- *Methylococcus*
  - is not a bacterial species carried by human beings or any animals like *E. coli*
  - exists in the wild such as in tropical rice field, soil, methane seeps on the ocean floor, hot springs, and natural gas field in high densities
  - density can be higher 10,000 bacterial cells per gram of soil in Malaysia because of Malaysia equatorial climate
- Standard operation protocols (SOP) with *Methylococcus* bacterial strains will be established in the MRSB U.S. facility following strict international guidelines and regulations
- The U.S. facility will be the first facility for developing and designing new projects, outcome of which will later be transferred to the MRSB Malaysian facility for scale-up production.

Friends And Foes

- Friend
  - The Institute for Genomic Research is sequencing *Methylococcus*
  - Sequencing completed in October 2004. Data is publicly available
- Clients
  - Research institutes, technology parks
  - Universities laboratories
  - Biotech companies
  - Pharmaceutical companies
  - Natural gas companies
- Competitor/Friend
  - Only known is a Norwegian research group supported by Norway National Natural Gas Corporation. Technology Park Malaysia (TPM) is starting this project as a nutraceutical project. Libraries can be shared to create a win-win collaboration.

Risks and Exit Strategy

- Work with Malaysia *Methylococcus* strains. Though this offers competitive advantages, discoveries can be strain-dependent
- Equipment have to be imported from US, Europe, Australia, may cause time delay
- Market penetration for each product may be different
- IPO (in year 5), or acquisition
  - Value ~ 100 million in five years.

Saving Lives
Worldwide

Thank you