Vol 13 | April 2020

MEDGENOME

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Internal Quarterly Newsletter

FROM
THE CHAIRMAN'S DESK

Hello Team MedGenome,

We are in the midst of World War III. At least we are not fighting amongst ourselves but against a common foe - a lowly virus which has given the powerful human species a big blow. The virus won the first round and we have taken huge losses but our spirit and strength in Science and Technology will enable us to overcome this. However, the wounds to the global economy will be severe, and it will take a few years to fully recover.

MedGenome has been lucky to be in a good position to handle this crisis. Due to the perseverance and hard work by MedGenome Co-founder and Board member Mahesh Pratapneni, we completed the current round of funding of $55M just before the crisis hit. More details about this on Page 5.

Though MedGenome does not have a focus on Infectious Diseases, our research team under the leadership of Dr. Sekar jumped into the fray and figured out the ACE2 variants that can help in predicting the individuals who would be more susceptible or resistant to the COVID-19 infection and published their results at https://biorxiv.org/cgi/content/short/2020.04.07.024752v1. Sekar and Kushal explain this in more detail in page 11. Dr. Ramprasad and team in India worked hard to get our lab operational during the lockdown and I have to sincerely appreciate and thank all our team members working from home and at the lab who ensured this.

I am also very happy to announce the appointment of Dr. Ramprasad as the CEO of MedGenome India. He will be fully in charge of our Diagnostic business P&L with Sales, Marketing, Operations, Finance & HR reporting to him. Ram's appointment to this position has been long due and will not come as a surprise to any one of you. From the inception of the company in 2013, Ram has been instrumental in building up our business and his leadership skills along with his dedication to science and operational excellence has won the admiration of the industry. Let us all assist Ram in taking MedGenome to higher levels of success as we continue to positively impact hundreds of lives every day.

Keep safe and healthy.

Yours truly,

Sam Santhosh,

Founder & Chairman, MedGenome

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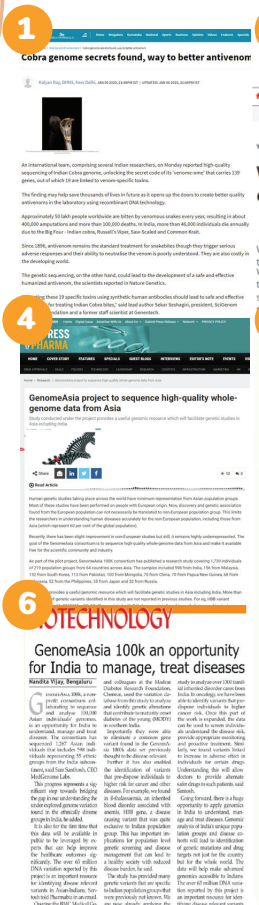

Cobra genome secrets found, way to better antivenom

An international team, comprising several Indian researchers, on Monday reported high-quality sequencing of Indian Cobra genome, unlocking the secret code of its 'venome-ome' that carries 139 genes, out of which 19 are linked to venom-specific toxins.

The finding may help save thousands of lives in future as it opens up the doors to create better quality antivenoms in the laboratory using recombinant DNA technology.

Approximately 50 lakh people worldwide are bitten by venomous snakes every year, resulting in about 400,000 amputations and more than 100,000 deaths. In India, more than 46,000 individuals die annually due to the Big Four - Indian cobra, Russell's Viper, Saw-Scaled and Common Krait.

Since 1896, antivenom remains the standard treatment for snakebites though they trigger serious adverse responses and their ability to neutralise the venom is poorly understood. They are also costly in the developing world.

The genetic sequencing, on the other hand, could lead to the development of a safe and effective humanized antivenom, the scientists reported in Nature Genetics.

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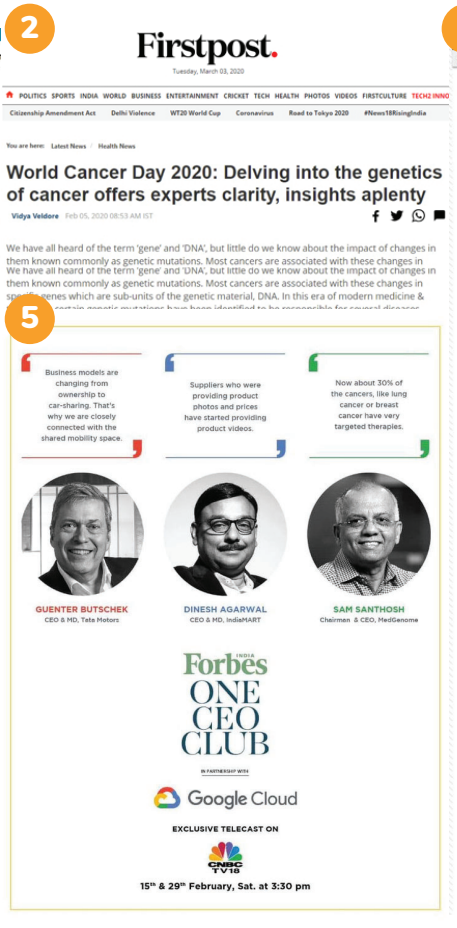

Firstpost.

Tuesday, March 03, 2020

POLITICS SPORTS INDIA WORLD BUSINESS ENTERTAINMENT CRICKET TECH HEALTH PHOTOS VIDEOS FIRSTCULTURE TECH2 INNO

Citizenship Amendment Act | Delhi Violence | WT20 World Cup | Coronavirus | Road to Tokyo 2020 | #News18RisingIndia

You are here: Latest News / Health News

World Cancer Day 2020: Delving into the genetics of cancer offers experts clarity, insights aplenty

Vidya Veldore Feb 05, 2020 08:53 AM IST

We have all heard of the term 'gene' and 'DNA', but little do we know about the impact of changes in them known commonly as genetic mutations. Most cancers are associated with these changes in

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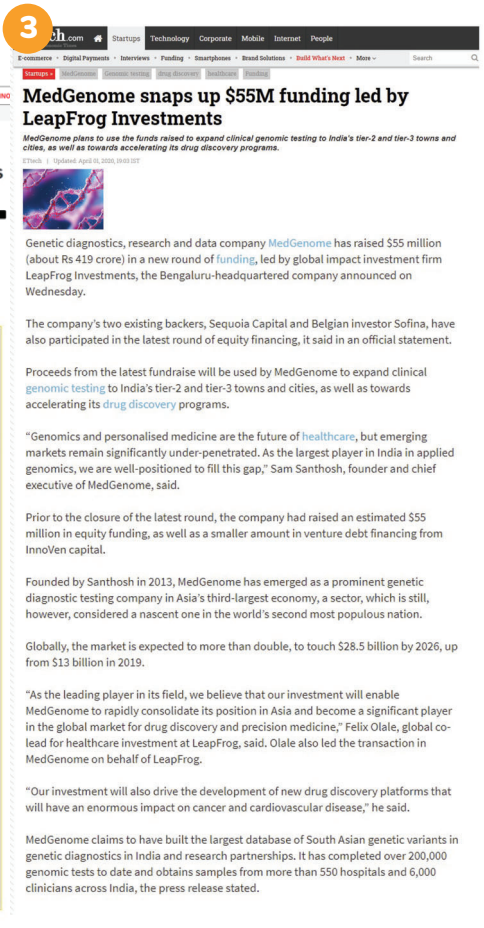

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Startups • MedGenome • Genomic testing • drug discovery • healthcare • Funding

MedGenome snaps up $55M funding led by LeapFrog Investments

MedGenome plans to use the funds raised to expand clinical genomic testing to India's tier-2 and tier-3 towns and cities, as well as towards accelerating its drug discovery programs.

ETtech | Updated: April 01, 2020, 10:03 IST

Genetic diagnostics, research and data company MedGenome has raised $55 million (about Rs 419 crore) in a new round of funding, led by global impact investment firm LeapFrog Investments, the Bengaluru-headquartered company announced on Wednesday.

The company's two existing backers, Sequoia Capital and Belgian investor Sofina, have also participated in the latest round of equity financing, it said in an official statement.

Proceeds from the latest fundraise will be used by MedGenome to expand clinical genomic testing to India's tier-2 and tier-3 towns and cities, as well as towards accelerating its drug discovery programs.

"Genomics and personalised medicine are the future of healthcare, but emerging markets remain significantly under-penetrated. As the largest player in India in applied genomics, we are well-positioned to fill this gap," Sam Santhosh, founder and chief executive of MedGenome, said.

Prior to the closure of the latest round, the company had raised an estimated $55 million in equity funding, as well as a smaller amount in venture debt financing from InnoVen capital.

Founded by Santhosh in 2013, MedGenome has emerged as a prominent genetic diagnostic testing company in Asia's third-largest economy, a sector, which is still, however, considered a nascent one in the world's second most populous nation.

Globally, the market is expected to more than double, to touch $28.5 billion by 2026, up from $13 billion in 2019.

"As the leading player in its field, we believe that our investment will enable MedGenome to rapidly consolidate its position in Asia and become a significant player in the global market for drug discovery and precision medicine," Felix Olale, global co-lead for healthcare investment at LeapFrog, said. Olale also led the transaction in MedGenome on behalf of LeapFrog.

"Our investment will also drive the development of new drug discovery platforms that will have an enormous impact on cancer and cardiovascular disease," he said.

MedGenome claims to have built the largest database of South Asian genetic variants in genetic diagnostics in India and research partnerships. It has completed over 200,000 genomic tests to date and obtains samples from more than 550 hospitals and 6,000 clinicians across India, the press release stated.

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GenomeAsia project to sequence high-quality whole-genome data from Asia

Study conducted under the project provides a useful genomic resource which will facilitate genetic studies in Asia including India

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Business models are changing from ownership to car-sharing. That's why we are closely connected with the shared mobility space.

Suppliers who were providing product photos and prices have started providing product videos.

Now about 30% of the cancers, like lung cancer or breast cancer have very targeted therapies.

GUENTER BUTSCHEK
CEO & MD, Tata Motors

DINESH AGARWAL
CEO & MD, IndiaMART

SAM SANTHOSH
Chairman & CEO, MedGenome

Forbes INDIA ONE CEO CLUB

IN PARTNERSHIP WITH

Google Cloud

EXCLUSIVE TELECAST ON

CNBC TV18

15th & 29th February, Sat. at 3:30 pm

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GENOTECHNOLOGY

GenomeAsia 100k an opportunity for India to manage, treat diseases

Nandita Vijay, Bengaluru

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For press articles, please click - https://diagnostics.medgenome.com/press/

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For Forbes One CEO Club- Interview with Mr. Sam Santhosh, talking about the journey of MedGenome and broad applications of genetic testing, please click - https://www.youtube.com/watch?v=0_jMUGRdnOA

MedGenome secures **US $55 million funding** led by **Leapfrog Investments**

Mahesh Pratapneni

Co-Founder & Board Member, MedGenome

We are glad to share that MedGenome has raised $55 Mn funding led by LeapFrog Investments, a private investment firm that invests in high-growth companies that create a positive impact on the world. Our existing investors Sequoia Capital and Sofina also participated.

This funding comes at a critical time in MedGenome's journey and will help fuel our expansion plans for diagnostics and further accelerate our "data to drugs" strategy. It validates MedGenome's core belief that genomics and personalized medicine are the future of healthcare.

In emerging markets, genetic diagnostics is starting to play an important role in enabling use of personalized medicine through early and accurate detection of disease for targeted treatment. As very limited genomic research has been done in emerging market population there is a significant unmet need in these markets. As India's largest player in applied genomics and our focus on Awareness, Access and Affordability, we are well positioned to fill the gap.

We have been the first to launch many innovative genetic tests in India, such as the first proprietary liquid biopsy (OncoTrack) for monitoring cancer treatment, a non-invasive prenatal screening test (NIPT) for pregnant women, carrier screening for couples planning a family, and whole-exome sequencing for cost-effective identification of rare mutations. Through this funding, we will continue our focus on science and bring many more cost-effective innovations to India and other emerging markets while helping many more families lead better lives.

MedGenome connect

Claria
Reproductive Genetics

Between January and March 2020, Claria organized 7 events, in which all zones have participated. With these events, we were able to reach out to nearly 300 clinicians, at a time when we are cementing the new version of Claria NIPT in the market, and willing to thrive on the surging need of this test in the market.

Dr. Priyadarshini's entry into MedGenome, and her in-depth understanding of Microarrays, will prove to be a shot in the arm for Claria. The early signs are promising.

Claria team members are striving hard to cross the 1000-sample barrier for the month, and we have picked up a good momentum. Focus over key clinicians, Gynecologists, Fetal Medicine Specialists, IVF specialists and Geneticists will be central to this achievement.

Tier 2 doctor CME in full swing @ Rewari on 21st January

Prima
Cancer Genetics

We at Prima have conducted a series of events and participated in a good number of high quality and scientifically important National/Regional Oncology Conferences, CME's/standalone Meetings, such as MAPICON (Jaipur), CME in Sassoon Hospital (Pune), Paediatric Haematology Conference (Bangalore), International Conference on Head and Neck Cancers (Kolkata), Young Radiation Oncologist conference (Coimbatore), 5th Molecular Oncology Conference (Patna), Bengal Society of Haematology (Kolkata), Ovarian cancer Updates (Bangalore), etc. The major therapies touch-based through these engagement programs were Oncology, Haematology and Primary Immunodeficiency.

Our team of experts, Dr. Ramprasad, Dr. Vidya and Dr. Arun made our participation remarkable with their involvement. The visibility and awareness on Prima and its offerings was further boosted by the sales team all across the cities in India.

Sales Team at ISHBT ERIC Conference at PGI Chandigarh

MedGenome connect

ACTIA
Inherited Genetics

The final lap of FY 2019-20, i.e. Q4 has been of great significance, as we participated in 3 major conferences, i.e. AOCN 2020 at Bangalore, APSID at PGI, Chandigarh and MDS-AOS Rare Movement Disorders conference at NIMHANS, Bangalore.

This was well supported with some of the key local events. Overall 4 CMEs were organized with a customer reach of about 200, mainly in the super specialty segment.

Each and every individual in the business team is geared up for enhanced performance and close this year on a high note. This will also give a strong foundation for Actia to have a headstart in the new financial year.

Team that made a difference at AOCN 2020, Bangalore

micra
Infectious Disease Genetics

MedGenome Micra conducted a CME in Chennai on SES- A must use tool for diagnosis of critical infections. Consultants as well as Pediatric Emergency specialists attended this event.

Well-attended Micra event in Chennai

From our US office

We are excited to launch the MedGenome 'Research Services Blog' (https://research.medgenome.com/blog/) as of March 2020. The blog will feature articles on relevant services/solutions/platforms/industry trends for our US and European business. The first article featured on the platform is on immune receptor repertoire profiling solutions that are offered by MedGenome. The platform is expected to boost search engine optimization (SEO) quality for MedGenome research website.

MedGenome colleagues are encouraged to take initiative and contribute towards the blog. You can share your blog articles with Vinay and Hiran @ mgus-blog@medgenome.com

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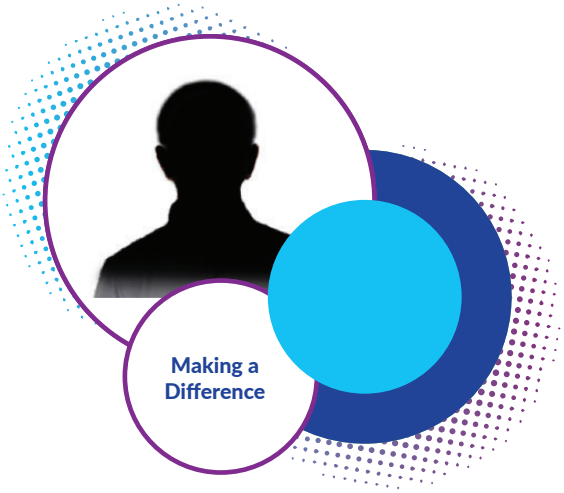
Last quarter we presented a poster titled **"Multiple Platforms for Single Cell Genomics to Enable Biomarker Discovery in Immunotherapy"** at SLAS Conference 2020, which had many interesting tracks encompassing cutting-edge science: Advances in Bio analytics and Biomarkers, Assay Development and Screening, Automation and High-Throughput Technologies, Biologics Discovery, Cellular Technologies, Data Analysis and Informatics, Drug Target Strategies, Micro- and Nanotechnologies, Molecular Libraries and Precision Medicine Technologies.

For more Information on our posters, please visit: https://research.medgenome.com/posters/

Making a difference

Genetic testing reveals multiple actionable mutations impacting the course of treatment in a patient with lung cancer

63-year-old Santosh Khurrana (name changed) felt the symptoms related to lung cancer and went for a consultation with Dr. Shyam Aggarwal. Before starting the therapy, he decided to test Santosh for presence of genetic mutation/s.



The tissue sample (FFPE block) was sent to MedGenome Labs, Bangalore for genetic sequencing. The report showed exon 19 deletion in *EGFR* gene. Presence of this mutation in the tumor confers sensitivity to first and second-generation *EGFR* tyrosine kinase inhibitors (TKIs): Gefitinib, Erlotinib and Afatinib. After confirmation of *EGFR* exon 19 deletion, patient was started on gefitinib therapy and as expected, Santosh showed improvement, symptomatically.

To Dr. Aggarwal's surprise, Santosh stopped responding to the treatment in a couple of months. Again, molecular testing was attempted to identify any resistant mutation acquired by the patient. The report revealed secondary mutation: *EGFR*-T790M which renders the patient resistant to first/second generation TKIs (Gefitnib/Erlotinib/Afatinib). Reacting quickly to this finding, Dr. Aggarwal changed the therapy to third generation TKI- Osimertinib and as expected, Santosh once again showed improvement, symptomatically.

The response of Osimertinib started to decline as well. A follow up molecular testing report showed found *EGFR*-C797S mutation. Presence of this mutation developed acquired resistance to Osimertinib. A deep-dive in the mutation type showed a mutation in cis-transformation with T790M.

Based on the finding, MedGenome suggested a unique combination of Brigartinib and anti-*EGFR* antibody. A study has shown that combination therapy of Brigatinib and anti-*EGFR* antibody is a powerful candidate to overcome Osimertinib resistance in triple-mutation-harboring cells (*EGFR* exon 19 deletion + T790M+C797S).

Summary

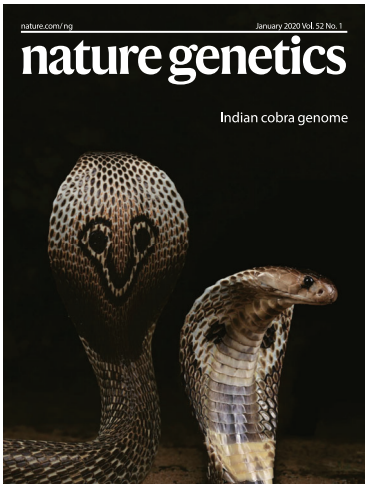
- Genetic testing reveals, step by step, a mutation that renders sensitivity and later a mutation that renders resistance for first and second generation TKIs
- Later genetic testing reveals a mutation that renders resistance to third generation TKIs
- MedGenome suggested a unique combination to overcome the resistance to third generation TKIs based on the findings

HIGHLIGHTS OF JAN 2020

MedGenome's Proud Moments

The Indian Cobra genome has been decoded!!

The article featured on the cover of the January 2020 issue of Nature Genetics



MedGenome launched
Direct to Consumer segment

ApnaGenome

at *KLF, Kozhikode.*

MedGenome received

accreditation from CAP

CAP ACCREDITED
COLLEGE of AMERICAN PATHOLOGISTS

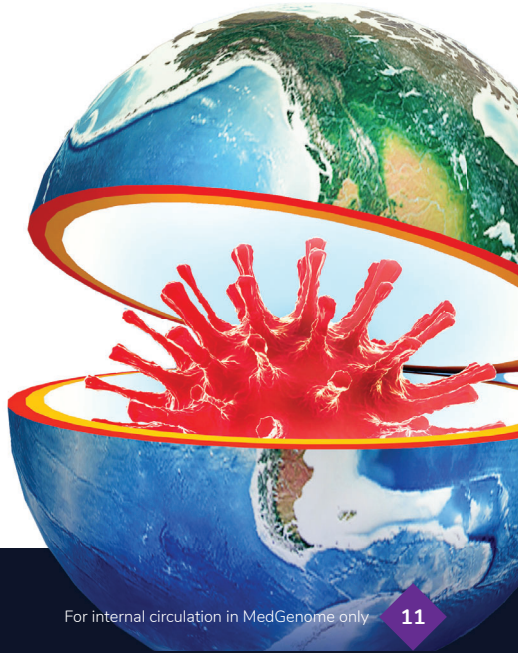
Can human *ACE2* gene variations alter susceptibility to COVID-19 virus?

Scientists unravel the mystery

Kushal Suryamohan (PhD)
Bioinformatics Scientist, MedGenome (USA)

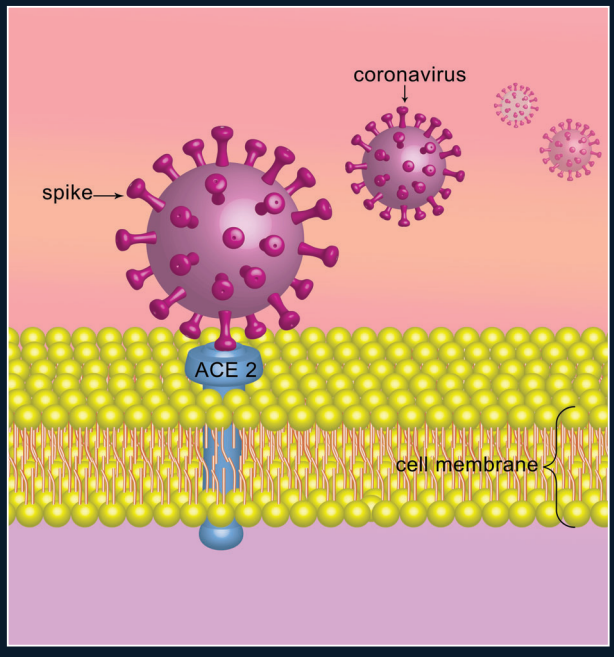
Sekar Seshagiri (PhD)
President, SGRF (India) | CEO & CTO, ModMab Therapeutics (USA)

The Coronavirus disease of 2019 (COVID-19) is caused by a highly contagious novel virus called the SARS-CoV-2. It was first reported in the Hubei province of China in late Dec 2019. While some infected individuals have been reported to be asymptomatic, others show mild flu-like symptoms to severe illness including high fever, chills, cough, diarrhea and pneumonia. In about 1-5% of the cases COVID-19 is fatal. As of 12 April 2020, more than 1.78 million cases of COVID-19 have been reported in over 180 countries, resulting in more than 108,000 deaths. While more than 400,000 people have recovered, we still do not fully understand if they will have long term immunity to the virus. COVID-19 has had a major impact on the economic front as well – the pandemic is presenting challenges to the global economy in an unprecedented manner with job losses hitting every sector. In India, the most vulnerable members of the population from the informal sector are already being affected disproportionately. From the scientific front the more we do to understand the virus and the disease it causes, we can help develop vaccine, therapeutics and diagnostics faster to combat this unprecedented pandemic



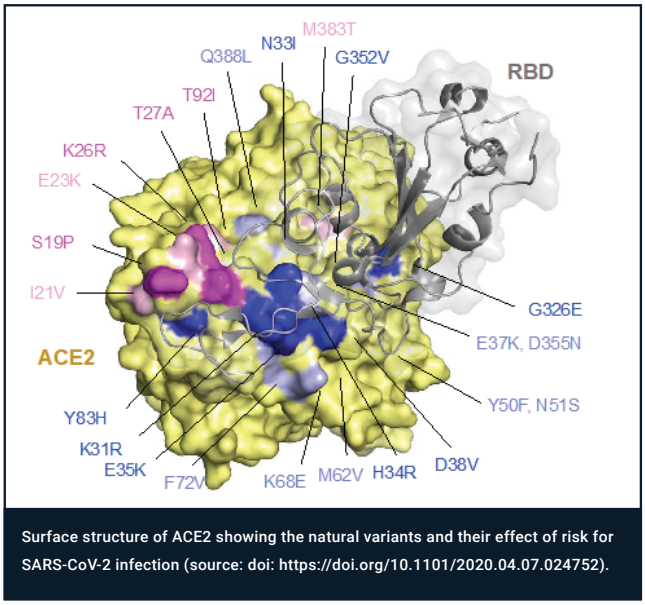
To begin to understand how the virus works, scientists first deciphered the SARS-CoV-2's code i.e. its genome sequence. The genome of this positive strand RNA virus can be imagined as a ~30,000 character sentence. The characters at each position in the sentence is one of four chemical bases or alphabets that make up the RNA world. By comparison the human genome, a 3 billion character sentence made of similar alphabets though from the DNA world, is 100,000x larger! Yet this tiny virus has taken us down and brought the world to a halt – how?

The virus is a submicroscopic tennis ball with little spikes (S-protein) jetting out of its surface. In the middle of the ball is the viral genome. The virus uses its S-protein to attach to a human host cell receptor called *ACE2* and sneaks into the cell. *ACE2* has a normal cellular role in managing blood pressure in our body. It sticks out of the cell like an antenna from the cell surface. The virus cleverly attaches to the *ACE2* and uses it like a door to get into the cell. Once inside the cell it co-opts and takes control of the cellular machinery to make tens of thousands of copies of itself and eventually gets out to infect other neighboring cells. As this process continues there is so much of the virus in the infected person's lungs, that the body expels it by way of cough and sneeze. The virus hitches a ride when the patient coughs or sneezes and travels in expelled body fluid droplets. If it finds a new human host it settles down, takes over the next victim and thus is spread. In this duel between the virus and the infected human, the host immune system comes to aid and deploys its antibody producing cells to fight the virus. If successful, antibodies produced neutralizes the virus and the person eventually recovers. This confers immunity against the virus and protects the person from future infections by this virus. Since the world has never seen this virus before, none of us are immune to it and that is causing the infection to spread at a large scale we watch.



What did we do at MedGenome while COVID-19 is raging ?

If I said we are in the business of genomics, it wouldn't surprise you. But we were not actually studying the COVID-19 virus genomics in detail until 3 weeks ago. The virus itself is only ~ 4 months into its incarnation. The world was and is scrambling to understand it at the molecular level so we can defeat it. In mid-march data from Italy and the high rate of death there compared to China suggested there might be genetic differences in individuals that may alter their susceptibility to the virus. One possibility was that there existed natural variants in the *ACE2* receptor, the antenna on the cells that the virus use to enter the cells, that made the virus stick more strongly to it and hence made it into the cells more easily. The converse could be true as well. We quickly swung into action and our cutting edge bioinformatics team mined data from multiple public genomics datasets from across the world including those from India (GenomeAsia 100k). The effort resulted in *ACE2* variation information from over 300,000 individuals across the world. Sifting through this we were able to identify variation in *ACE2* that were located in positions that are key for the virus S-protein interaction. Using other evidence and structural analysis with our collaborators, we were very quickly able to identify *ACE2* variants that are predicted to make individuals carrying these to be more susceptible to the virus or others who might be protected. While this type of variations is not common (<1%), are likely to be a factor that lead to the varying symptoms we observe. The results from this study was published in the Bioarxiv recently, while the paper undergoes peer review. It will enable clinical studies that can correlate clinical symptoms with the reported *ACE2* variation types.



Surface structure of ACE2 showing the natural variants and their effect of risk for SARS-CoV-2 infection (source: doi: https://doi.org/10.1101/2020.04.07.024752).

We still have some ways to go before this pandemic ends. As you might have heard many groups are working on vaccine and therapeutics. Besides identifying people that may be vulnerable due to specific *ACE2* variations, the findings from the study can be used to make a drug for COVID-19 treatment. Like the *ACE2* on the cell surface we can make a modified *ACE2* carrying the stickier variants we have identified and express it recombinantly like insulin in cell culture. The purified *ACE2* can be given to patients with perhaps serious symptoms as a treatment. It will act like a sink, adsorb the virus and prevent it from sticking to *ACE2* on the cells and invading it – it's a way to beat the virus in its own game by supplying a rationally engineered decoy *ACE2* variant.

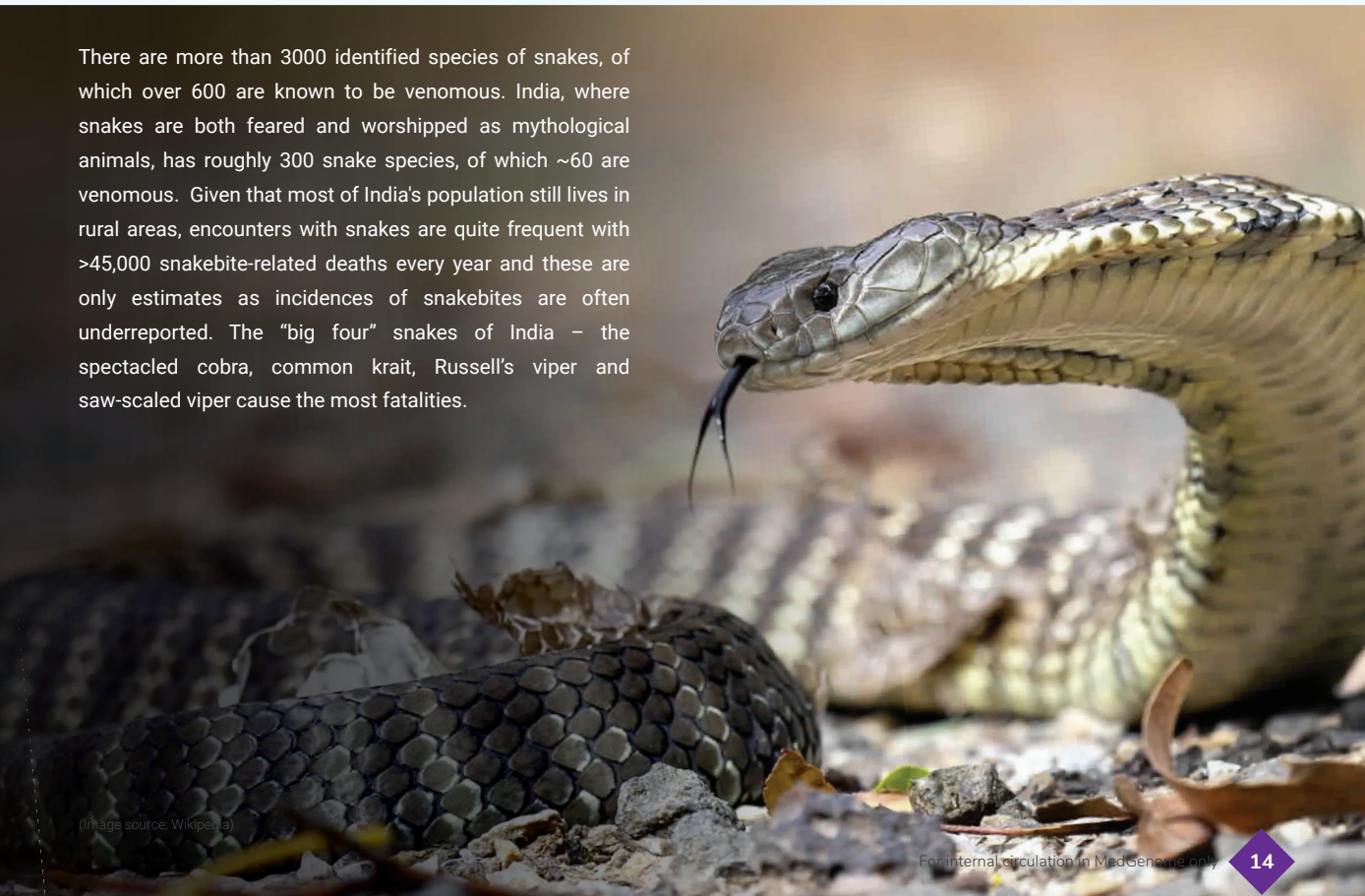
We are very happy that we could do this type of work so quickly and all of this would not be possible without the scientific talent and infrastructure at MedGenome. The team now is turning to another question – can the COVID-19 SARS-CoV-2 infect animals? You heard that a tiger in New York Zoo was infected with the COVID-19 virus? Is it real? Can a cat or dog get infected? How about monkeys, our close relatives? We are zeroing in on the answers to these questions and perhaps will be able to tell you more in a future newsletter. In the meantime, please stay safe and keep well!!

Snake Genomics

Kushal Suryamohan (PhD)
Bioinformatics Scientist, MedGenome (USA)

For the majority of people, the mere mention of snakes conjures involuntary shivers! These stealthy critters have a forked tongue, unblinking eyes and either have fangs that deliver venom to immobilize/kill prey or strong muscles to asphyxiate. Snakes have been around for millions of years, and have used this time to become incredibly effective predators and can be found on all continents except Antarctica. Beginning over a 100 million years ago, snakes diverged from lizards, lost their legs and evolved into smaller and faster hunters to catch quick-moving prey. Rather than expend a great deal of energy to forage for food, many snakes developed venom - a complex chemical cocktail of proteins and enzymes designed to kill or incapacitate the prey even before ingesting their meals. The toxins in these venoms have been refined over millions of years to target highly specific pathways that affect their prey's vital bodily functions. Some toxins are neurotoxins while some disrupt hemostasis and several others that are cytotoxic. Some snakes are so dangerous that people die from such encounters. According to the most recent report by the World Health Organization, about 5 million people are bitten by snakes and ~100,000 are killed annually.

There are more than 3000 identified species of snakes, of which over 600 are known to be venomous. India, where snakes are both feared and worshipped as mythological animals, has roughly 300 snake species, of which ~60 are venomous. Given that most of India's population still lives in rural areas, encounters with snakes are quite frequent with >45,000 snakebite-related deaths every year and these are only estimates as incidences of snakebites are often underreported. The "big four" snakes of India – the spectacled cobra, common krait, Russell's viper and saw-scaled viper cause the most fatalities.



(Image source: Wikipedia)

While antivenom, the only currently approved form of treatment for snakebites, is freely available in public hospitals, there are several issues with the current practices in antivenom manufacturing, often resulting in anti-venom that is poorly efficacious. One reason for this is snake venom and its potency differs between species, and even between snakes of the same species between regions. For instance, while doctors have been known to administer 2-3 vials of a certain antivenom against a species of snake in one part of India, more than 25 vials of the same serum are required to treat a victim bitten by the same snake in another part of the country. Another reason for this lack of efficacy is the archaic technology used for antivenom manufacture. Antivenom manufacturers still use a technology that was first pioneered ~120 years ago (about 30 years before penicillin was discovered by Alexander Fleming). This method relies on the use of snakes for milking their venom glands to extract venom. Small amounts of venom are then repeatedly injected into horses to create an immune response. Antibodies are then extracted from the blood and packaged as antivenom (with a few minor steps in between that help extend the antivenom shelf life). Needless to say, this is a laborious and expensive process. More importantly, over 70% of the antibodies in this antivenom cocktail do not target the toxins that cause the most damage in snakebite victims. This is because when antibodies are extracted from the horse's blood, you do not only find those that recognize the snake toxins but also countless other antibodies are recovered which have no therapeutic effect on the snakebite as these antibodies recognize bacteria, viruses, hay, dust, and other environmental stimuli the horse may have been exposed to. Therefore, such antivenoms are typically less potent and necessitate administration of multiple doses of antivenom per treatment. Another consequence of this is that the antivenom can cause adverse reactions in the patient/victim including hyperallergic reactions such as serum sickness, kidney failure and anaphylactic shock, which can kill the snakebite victim if the snake does not do so first. Another critical drawback is the poor efficacy of such antivenoms - many snake venom toxins are small proteins and are poorly immunogenic and therefore are not attacked by the horse's immune system.

Given these drawbacks, several alternative antivenom manufacturing methods have been proposed. One such approach that has gained increasing attention is the use of phage display technology. Phage display technology is a high-throughput approach to discover human antibodies specific to different antigens. Several antibodies discovered using phage display technology have been approved for use as drugs to treat a number of human diseases, ranging from cancers to autoimmune disorders. Using this approach, it is now feasible to develop humanized antibodies that can target key proteins, like potent toxins, to create effective and safe antivenom. In lieu of relying on snakes for venom, knowledge of the toxins and their genomic coding sequences for a given species will instead allow for the synthesis and expression of venom components using recombinant DNA technology. These can then be used as antigens for antibody discovery. A cocktail of such antibodies against the most potent toxins

(Image source: Wikipedia)

(Image source: Wikipedia)

(Image source: Wikipedia)

can be combined to yield a synthetic antivenom of a defined composition. Importantly, these humanized antibodies will not elicit an immune response from patients and can be produced using standard lab approaches for drug manufacture. Equally important, this approach will lead to a more humane and cost-affordable approach to antivenom manufacture as it does not require maintaining a collection of snakes for venom extraction or horses for antivenom development.

While the above mentioned methods are superior for antivenom development, large animal-based antivenom production, using extracted snake venoms, still continues to be the standard practice. This is due to several factors including socio-economic barriers, low funding for research initiatives, the complexity of developing an alternative treatment, and low economic incentives for pharmaceutical companies to develop antivenoms. In 2018, snakebite envenoming was added to the World Health Organization's (WHO) list of Category 'A' Neglected Tropical Diseases in 2017, thereby bringing renewed attention and focus on promoting research and development efforts into novel snakebite antivenom therapies.

A significant hurdle in developing nextgen antivenom is the gap in our understanding of snake venom. Much of our current knowledge on snake venoms is based on proteomic studies and they have provided an incomplete picture of the venom components. Mass spectrometry of venom relies on a good database of proteins to accurately identify the constituent components. Given the limited genomic or transcriptomic reference datasets for venomous snakes, this database of venom proteins is not comprehensive.

Our impetus to get involved in snakebite and antivenom research was fueled by this gap in antivenom manufacture technology. Given MedGenome's expertise in the NGS space, we leveraged this experience and utilized several genomics sequencing technologies including long-read, short-read sequencing platforms, optical mapping and chromosome conformation capture methods to produce the first high-quality reference genome of the Indian cobra. This study was recently published in Nature Genetics and was featured on the cover of the January 2020 issue. Besides the genome, we also published a comprehensive catalogue of venom genes for this medically important snake. An integrated analysis of genome, transcriptome and venom proteome of the Indian cobra revealed 12,346 genes that were expressed in the venom gland that included 139 toxin genes from 33 different toxin families. From this list, we identified 19 genes that were primarily expressed in the venom gland. Using proteomic data from the venom, we confirmed the presence of 16 of these toxins. It is likely that these toxins form the major components of this species' venom and targeting these venom-specific toxins using synthetic antibodies should neutralize the major toxic effects. This information can be used for rational design and expression of toxins of interest using recombinant DNA technology. Recombinantly produced toxins can then be used for developing synthetic antibodies using phage display technology. Once identified and tested, the resulting synthetic human antibodies against the different toxins can be produced on a large scale and combined to yield a safe and effective antivenom. We envision such an antivenom can be manufactured in a


(Image source: Wikipedia)


(Image source: Wikipedia)

cost-effective manner and be made more accessible across India. This approach will modernize antivenom development and set the stage for the generation of a broad spectrum antivenom against the 'Big Four' Indian snakes

Our study has given insights into previously unknown genetic structure and variations in venom genes within a given snake species. This study provides a useful genomic resource which will facilitate studies of venom biology, evolution, drug discovery and antivenom research in Asia and across the world.

Another aspect of our venture into snakes is the fact that despite their deadly nature, venom is one of nature's most beautiful paradoxes. By design, venom is meant to kill, and it does this job frighteningly quickly and efficiently! Yet, the same properties that make it deadly can also be harnessed to provide potent healing. Several components of venom often target the same molecules that medicines target to treat diseases. Indeed, out of the ~1,000 venom toxins that have been analyzed by scientists so far, about a dozen drugs have been developed and brought to market. There are already six drugs approved for use by the FDA (Food and Drug Administration) in the USA – all derived from venom. To date, the FDA has approved seven drugs derived from animal venom for conditions such as high blood pressure, heart conditions, chronic pain, and diabetes. Ten more are currently in clinical trials while many others are in pre-trial stages. And we have only barely scratched the surface - with an estimated 300,000 venomous animals found across the world and ~50-60 unique toxins in each species, there are ~20 million potential toxins, each with its own targets and effects that remain unexplored. While snakes are our primary species of interest for venom research, we are also studying other venomous creatures, from venomous caterpillars to jellyfishes, centipedes, scorpions and many more. Our goal is to catalogue the genomes and venom of these species and thus create a rich resource for drug discovery. Stay tuned for more updates on the fascinating world of venomous animals.

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By S. Lakshmi (PhD)
Senior Scientist, MedGenome Labs (India)

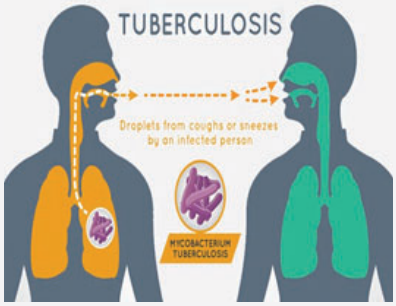
What Do We Know About Tuberculosis?

Tuberculosis (TB) is a potentially serious infectious disease that mainly affects the lungs (called Pulmonary TB), but it can also affect almost any organ in the body. Once rare in developed countries, tuberculosis infections began increasing in 1985, partly because of the emergence of HIV, the virus that causes AIDS. India has the largest number of tuberculosis (TB) patients worldwide, accounting for over 25% of global cases.

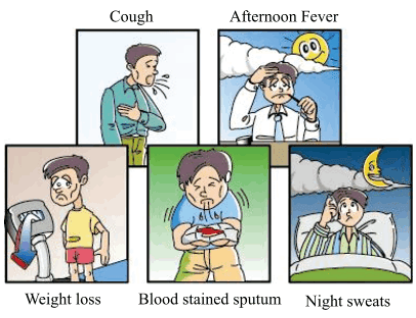
Medications are available to treat TB and is administered as prescribed by the clinician. Depending on the medication(s) prescribed, the duration can be from four to nine months or more. Resistance to TB drugs is a formidable obstacle to effective TB care and prevention globally. Multidrug-resistant TB (MDR-TB) is multifactorial and fuelled by improper treatment of patients, poor management of supply and quality of drugs, and airborne transmission of bacteria in public places. As per the World Health Organisation (WHO) 2019 report, Drug resistant TB continues to be a public health threat. In 2018, there were about half a million new cases of rifampicin-resistant TB (of which 78% had multi drug resistant TB), and India stands one among the three high-burden countries accounting for 27% of the MDR/RR TB cases.

How and who are borne to develop the TB Disease?

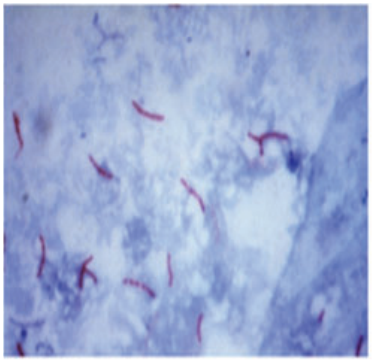
TB is transmitted through the air as tiny droplets when a person with TB sneezes, coughs, talks, laughs, or sings. Many a number of people are exposed to TB bacterium without becoming infected. Some can also become infected but may not develop active disease — this is called latent TB infection (LTBI). LTBI means that the immune system can contain TB infection and prevent active disease. Active TB disease happens when TB infection overwhelms the immune system, and the bacteria begin multiplying and cause disease.

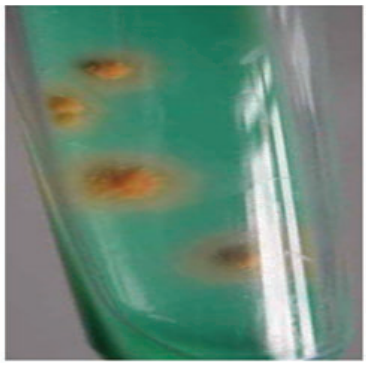


Some symptoms of Active TB disease are -



Here is the TB Bug we observe under the Microscope and Culture





Mycobacterium tuberculosis (Mtb), the causative organism of tuberculosis, is a slow growing bacterium taking several weeks (4 to 6 weeks) for culture growth. This delay in diagnosis could worsen illness severity, prolong patient suffering, increase the risk of patient death, and facilitate the transmission of the disease (if smear-positive pulmonary TB) to close contacts

Diagnosing TB and the Challenge we have

There are now 6 WHO-endorsed tests for detection of drug resistance: liquid culture, line-probe assays (LPA/Hains Test), the microscopically observed drug-susceptibility (MODS) assay, nitrate reductase assays (NRAs), colorimetric redox indicator (CRI) methods, and Xpert MTB/RIF (GeneXpert/CBNAAT test). Diagnosis of Mtb by culture remains the gold standard while Xpert MTB/RIF test and LPA, the two widely used molecular tests are replacing by their wide usage both by the public and the private sectors.

Cultures take several weeks to diagnose Mtb varying from 6 days to 8 weeks. This is laborious and needs expert training. Xpert MTB/RIF could be placed in peripheral laboratories but only for identification of single drug (rifampicin) resistance with a reported sensitivity of 98% in smear positive cases and 70% in smear negative cases.

Line-probe assays could be placed at an intermediate level in the healthcare system but have low sensitivity on smear-negative sputum samples. Despite the advantage of these molecular tests on the timeline of diagnosis with direct specimens, the limitation of these are the detection of resistance to limited loci and does not eliminate the need for conventional culture and drug susceptibility testing (DST).

Why do we need NGS?

Whole-genome sequencing (WGS) has become a common technique for the investigation of pathogenic and environmental bacteria and has been used to address various aspects of tuberculosis. Culture-based WGS has been shown to reliably predict not only the drug resistance but also explain the differences in transmissibility between strains, or why some strains are more virulent than others or more prone to the development of multidrug resistance. In spite of the wide application of this technique, WGS has not yet become a predominant diagnostic in high-burden settings, due to the cost and time associated with culture growth.

Whole genome sequencing (WGS) offers the opportunity to screen not only the loci included in rapid molecular tests but also other known resistance-associated loci not screened by them. This enables the identification of new drug resistance-associated mutations that are not explained by currently available diagnostics at significantly shorter turnaround time. WGS performed directly on sputum samples so far has had limited success due to low Mtb load in sputum, resulting in low sequencing depth, which may under-identify drug resistance, with the presence of contaminating human and bacterial DNA, including non-tuberculous mycobacteria (NTMs) further adding analysis challenges.

To address the above challenges, we at MedGenome performed WGS on uncultured direct sputum samples to detect Mtb and identify drug resistance using a targeted enrichment-based method, followed by an improvised analysis technique to isolate Mtb-specific reads. The resistance variants predicted by this method were validated by comparing results to alternative technologies like Xpert, LPA, and culture-based phenotypic DST on the same samples. The Validated Test is the newly launched TB test - **SPITSEQ – Whole Genome Sequencing of Mtb from Direct Sputum.**

SPITSEQ, a Single test for diagnosis and drug resistance prediction, is a culture- free WGS method. This has 100% sensitivity and 98.4% to resistance variants profiled by line probe assay (LPA) and 97.7% accuracy with the phenotypic drug susceptibility tests for six anti-tuberculosis drugs using as little as 5ng of sputum DNA. This assay is a comprehensive drug panel revealing the mutations not only to the currently available anti TB drugs but also the newer drugs that are being validated.

Drug Resistance Associated Target Genes and Mutations

From a cost perspective, WGS is more expensive than individual tests for smear, Gene Xpert, or LPA. However, WGS, as a standalone replacement for all these tests, along with culture-based DST, is more reasonably priced with an advantage of the lesser turnaround time.

In light of the strong performance of this technique to predict drug-resistance compared to current tests and the greater information obtained from WGS, this method represents a possible tool for implementation in low-income, high-TB burden countries.

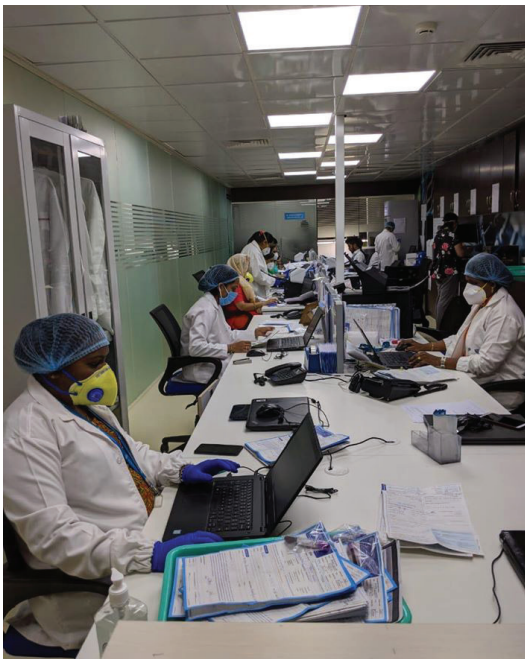
MedGenome Publication on the New Assay

Soundararajan *et al,* Whole genome enrichment approach for rapid detection of *Mycobacterium tuberculosis* and drug resistance-associated mutations from direct sputum sequencing. *Tuberculosis* 121 (2020) 101915.

COVID-19 BATTLEFIELD

THANK YOU

TO OUR BRAVE SOLDIERS



The world is in the grip of an unprecedented coronavirus disease pandemic impacting every aspect of our lives and people are struggling with ways such as containment procedures, necessary lockdowns, travel restrictions, and behavioural changes to deal with the impact.

As the Covid-19 crisis began in India, MedGenome reacted swiftly and issued the first advisory on 5th March alerting employees of the disease and the precautions to be taken. All non-essential travel was suspended, and many employees were encouraged to work from home. As the number of cases in the country and Karnataka increased, a further contingency plan was developed and implemented. Several arrangements were made in parallel to continue operations to process patient test samples on time. Facilities such as accommodation and transportation were provided to all relevant employees to ensure business continuity. Wearing extra PPE like N95 masks by lab team, practicing social distancing was made mandatory. Essential services pass from police were facilitated to employees who were attending the office during lockdown.

We at MedGenome, are committed to many doctors and patients who rely on our test results to guide their treatment. **Our heartfelt thanks to our brave colleagues** for working to ensure that our diagnostics services are getting to those who need them.

We are also thankful to all our brave soldiers from various sectors such as healthcare, essential products, law & order, etc. for their tireless efforts in fighting this war.

From our Colleagues

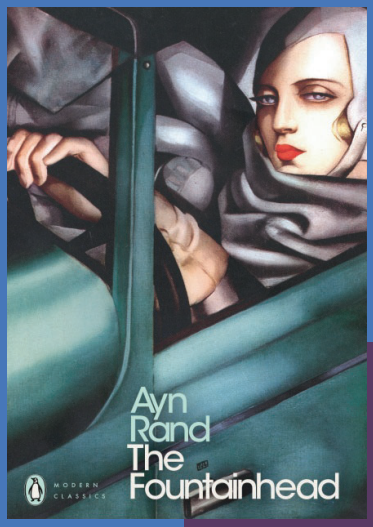
Verbum

Book: ***The Fountainhead***

Book review by : ***Gargi Vyas,*** *Bioinformatics*

"Dean : ***"My dear fellow, who will let you?"***

Roark : ***"That's not the point. The point is, who will stop me? "***



The Fountainhead is a book about Howard Roark's conviction and his incredible will as he pushes ahead even when there appears to be no way forward. Roark is an egotist and a righteous architect who thinks of his buildings as an extension of himself. Each and every piece of his architecture has its own unique utility and its assemblage distinctive. He is striving to change the course of architecture, from old renaissance to "modern". Throughout his career, he is shot down by almost everyone and is seen as a dissident of the very core of architecture. On the other hand, his peer Peter Keating becomes the focus of the architectural society and is seen as a messiah who will save the classic architecture from perishing. Keating, an architect who lacks originality of thought, is not able to conceive any plan of any building without copying it from elsewhere, rises through the architectural world by giving all his clients buildings with grandeur and splendour, but turns to Roark for design problems.

Ellsworth Toohey, a socialist architecture critic who uses his influence to promote his political and social agenda, tries to destroy Roark's career and enhance Keating's. Gail Wynand, an industrialist who has risen from the ashes of the city befriends Roark and then betrays him when public opinion doesn't go in his direction.

The one main female character, Dominique Francon, daughter of the famous architect Guy Francon, is probably the complex character in the book. Each one of her actions connotes something different. Dominique believes that men can achieve their greatest self with their work and therefore loathes the likes of Peter Keatings and Ellsworth Tooheys. She is consequently a philosophical pessimist believing that the world will not let the great original minds survive and hence renounces her pursuit to the ethical values.

"Integrity is the ability to stand by an idea. That presupposes the ability to think. Thinking is something one doesn't borrow or pawn."

Howard Roark is an Objectivist. Objectivism is a philosophical ideal that was created by Ayn Rand herself. An objectivist is a person who achieves true happiness from his works, attitudes and behaviours. Roark will not work with any client unless they agree to build on his terms, and his terms are that the building must be built as he designed it with absolutely no change. His designs were more of a practical and less aesthetic nature, modernistic as they called it. He wouldn't build for his clients, he would build so that he could bring the buildings to life. People saw Howard Roark but Howard Roark saw no one. Ayn Rand has explored objectivism, the belief that certain things, especially moral truths, exist independently of human knowledge or perception of them. According to Rand, objectivism is "the concept of man as a heroic being, with his own happiness as the moral purpose of his life, with productive achievement as his noblest activity, and reason as his only absolute."

"Self Sacrifice? But it is precisely the self that cannot and must not be sacrificed"

The best villain is the one who does not think himself villainous. Toohey deceives his victims by posturing as a humanitarian, but the code he preaches — that of self-sacrifice — is utterly destructive. Under the guise of offering spiritual guidance, Toohey convinces his followers to give up the things most important in their lives — their values. He tells them that virtue lies in selflessness, in the renunciation of personal desires, and that they must exist for the sake of others. He succeeds with a number of weak-willed individuals, who then surrender the things and persons most precious to them. But when a man gives up his values, he necessarily gives up that with which he formed them — his own thinking.

"The selfless man is the one who does not think, feel, judge or act"

Peter Keating is a conformist. He surrenders his judgment and allows other people to dominate his life. In this regard, he is the story's foil, a contrast to its hero, Roark. An aggressive social climber, Keating desires prestige above all else. Because Keating attempts to rise to the position of partner in the country's most prestigious firm — and because he uses any means necessary to attain this end, including flattery, deceit— he is conventionally thought of as selfish. But Ayn Rand presents a revolutionary analysis of such a status-seeker's nature. Peter Keating, she says, is selfless. He sacrifices the things that he wants in order to please others. He surrenders his own loves and values in an attempt to win social approval. He relinquishes autonomy and permits others to dominate his life. Ayn Rand argues that in order to be selfish a man must be true to his self — and that the self is fundamentally a man's values along with the thinking he does to form them. This is the meaning of Keating's life. He is selfless in a literal sense — he is without self.

"He bent the branch slowly into an arc. "Now I can make what I want of it: a bow, a spear, a cane, a railing. That's the meaning of life - your work. The material that earth offers you and what you make of it""

The Fountainhead is a celebration of the individual and creativity. It holds man's creative mind as sacred, and consequently admires the great original thinkers of mankind — the artists, scientists, and inventors, such as Michelangelo, Newton, and Edison. In Rand's fiction, she illustrates the heroic battles such great individuals have to go through, both to develop their new ideas and methods and to struggle against a conservative society that rejects them. Rand indicated that the primary theme of The Fountainhead was "individualism versus collectivism, not in politics but within a man's soul".

From our Colleagues

By : Angela Devanboo, Operations

One of the many villages in Jebel Shams, Oman

A distant view of University of Glasgow

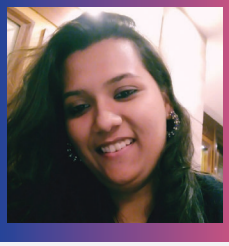
Glasgow during fall

Mountainous terrain of Jebel Shams, Oman

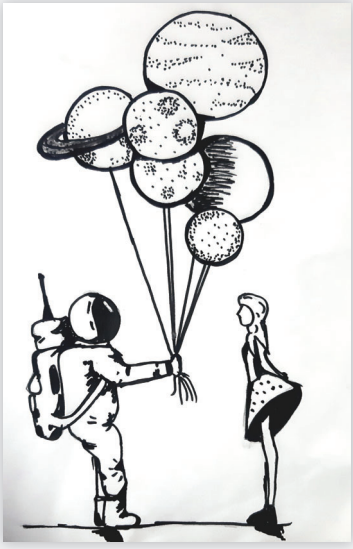
From our Colleagues

Art meets Science

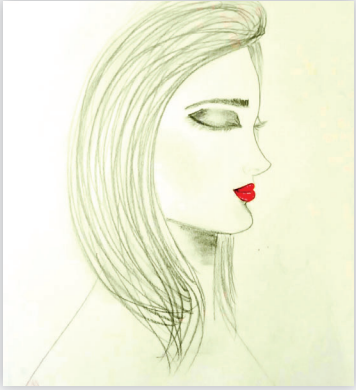
Every science touches art at some points—every art has its scientific side. — ***Armand Trousseau***



By: Antra Mittal
Bioinformatics Analyst



By: Kamalika Das
Events & conference



Our employee's little Picasso :)

By: Ananthajith M S (10 years)
DNA of Santhosh Kumar, Admin

By: Ananthajith M S (10 years)
DNA of Santhosh Kumar, Admin

By: Dhyan C M (8 years)
DNA of Sindhu C M, Procurement

By: Dhanish C M (8 years)
DNA of Sindhu C M, Procurement

Employee connect

WELCOME

Our New-Joiners


Abi Salih


Ananya Ghosh


Anoop Kumar P


Antra Mittal


Atul Vishnu Shivhare


Deepak Shukla


Deepika M


Nirali Desai Rajan


Ganigara Bindu Sree


Girish Ratnakar


Himadri Shekhaar


Karthikeyan Jothi


Kaviyarasu S


Mamilla Geervani


Manju Lakshmi


Rajarshi Bhattacharjee


Rajasekar


Ritika Chauhan


S Sumathi Angel

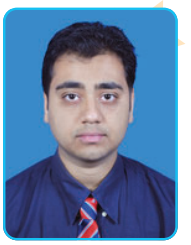

Senthil Kumar P


Vishram Pralhad

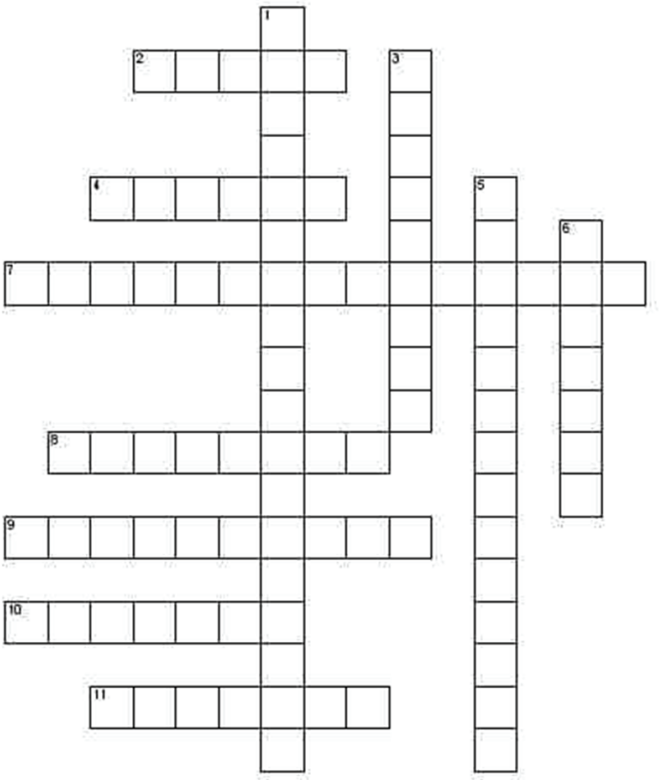

Sai Yuva Sandeep


Goutham U


Manjunatha Guptha


Soham Ghosh

Employee connect



Across

5. He inserted a gene from an African clawed toad into bacteria and birthed genetic engineering

4. These hormones allow cows to produce more milk

7. Industry that benefits from genetic engineering

8. The environment is unable to destroy these

9. Organism modified by introduction of foreign DNA

10. Dormant genes

11. Percent of genetic engineering is focused on promoting agriculture

Down

1. How to manipulate a genome to alter cell function?

3. The first genetic engineering company

5. A technique used in biological vectors

6. Small ring of DNA

*Kindly mail your answers by 15th May 2020 to **editor@medgenome.com**. The first two people to answer the puzzles correct will be featured in the next edition of our newsletter.*

Photo feature

Women's Day and Birthday celebrations

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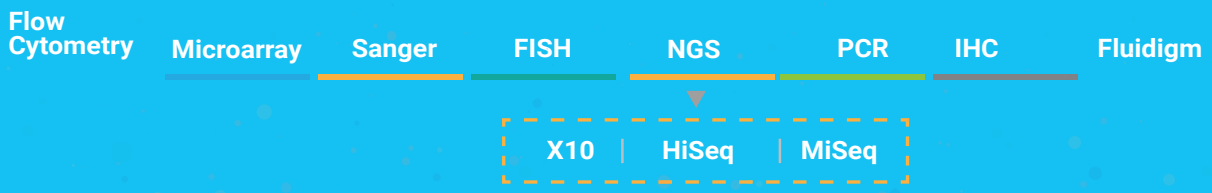

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