MEDGENOME

Vol 24 | January 2023

GeKNOWme

Internal Quarterly Newsletter

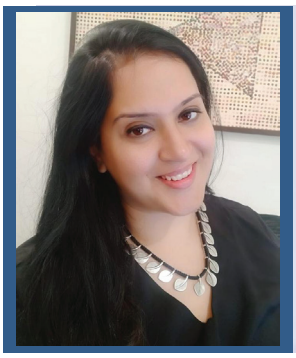
Cover Story

Genetic alterations in non-coding regions: the hidden players in cancer genomics

Scientific Article

Immune Risk Profiling for Anti-drug Antibodies following treatment with Monoclonal Antibody-based therapeutics

WORDS FROM THE **FRONTLINE**



Dipti Manchanda
Associate Director, HR

Dear MedGenome Team !!!

After 15 years of being an HR professional, I still have the same passion as I had when I started my journey in the world of Human resources. The key mantra behind this is “I love my profession." Life becomes easy when you fall in love with your profession as you always try and find the best in it, yes there can be setbacks, but a good relationship is one where you see good and bad times together, it helps strengthen the relationship.

My journey at MedGenome in the last few months have been absolutely challenging and exciting at the same time. My team has been my backbone and I would like to take this opportunity to thank them for all their support and patience that they have shown in integrating me into the system.

As a pioneer and first mover in its space, MedGenome has provided unique growth opportunities for its employees and this industry in general. To work alongside such brilliant minds is absolutely an honor. The leadership team is always striving to think in the best interest of the employees and one such case is how everyone came together during the pandemic to seamlessly run operations without compromising on the health and safety of our employees.

Luckily this challenging period of pandemic is behind us and we are marching forward to the new normal of being back to our office locations close to our colleagues yet again building impromptu connections, socializing as we yearn for interactions and shared experiences that come naturally just by being together. This also helps in creating a more cohesive company culture, wherein we have the opportunity to build relationships, bringing in a sense of camaraderie as opposed to in a remote setting. Getting deeper into this subject lets understand the key benefits of working together at a common workplace, which are:

Increased Collaboration:

While we are all together in the same working space trying to solve a problem or address situations together, in-office collaboration allows for smoother and faster solutions. In addition, it provides a perfect platform to constantly come together, celebrate our wins - big and small, and even have those much-needed informal connections. Returning to the office full-time or on a hybrid basis will help re-establish and foster a sense of workplace community and connection.

Rejuvenated Rhythm of Work:

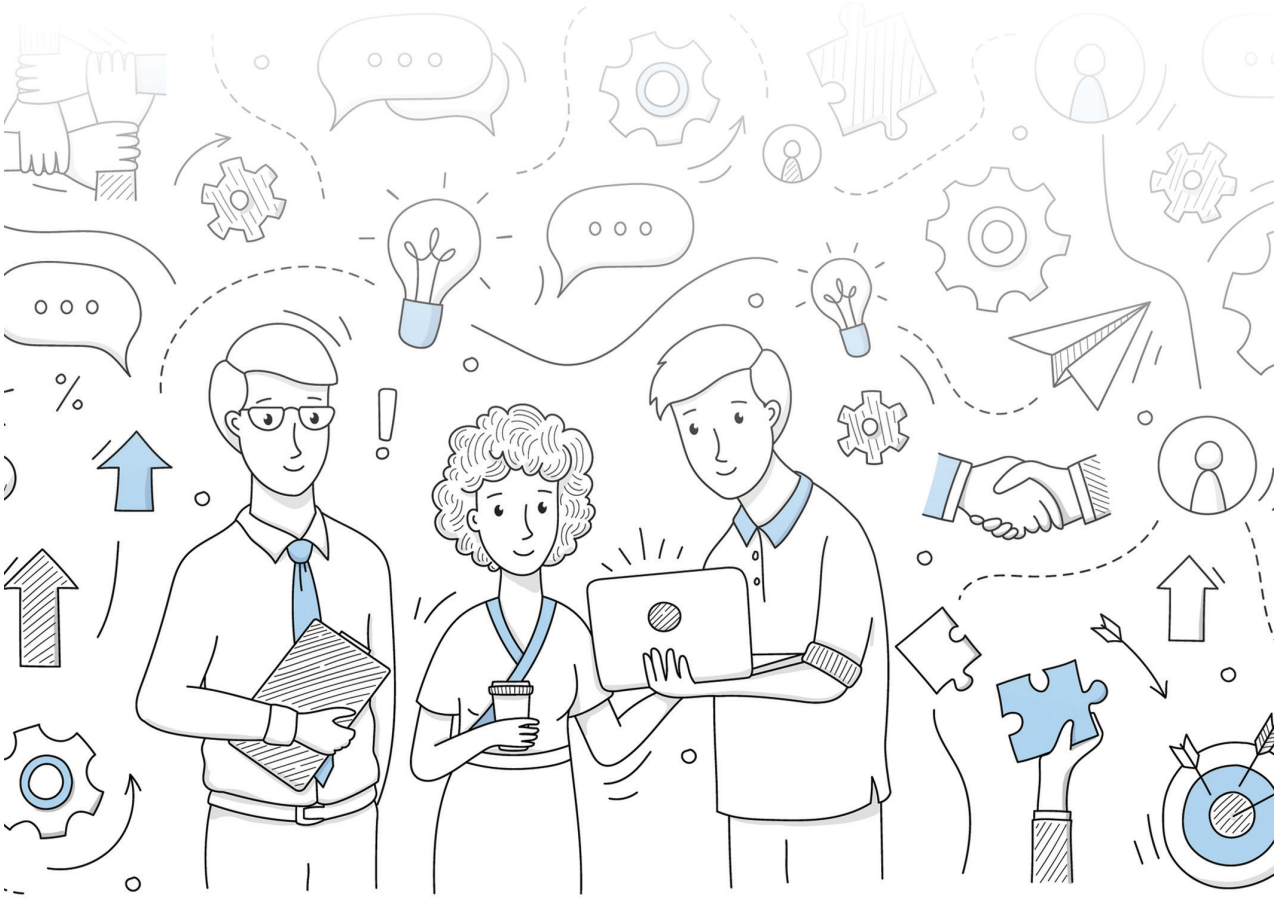
Coming to the office sets boundaries with our family and helps establish constructive routines. Being in a dedicated workspace can signal to the brain that it is time to focus on work while leaving the office at the end of the day can signal the transition to personal time.

A Healthier Routine:

Social interactions play a tremendously positive role in our happiness. Getting up, going to work in a different setting, and coming home—that's conducive to a more creative and active work-life balance.

Towards the end, I would like to conclude by sharing some positive news to look forward to by everyone. As an HR team at MedGenome we hold automation as a central theme for all our executions and to the same effect we are trying to eradicate the manual interventions both for employees and for the HR team, to this effect you will see a new HRIS system which will be soon implemented.

So on that note since we live in a hashtag world let's make the theme of this year at MedGenome as #The way to get started is too quit talking and begin doing



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Most Talked About

The News

MEDGENOME NEWS — October to January 2023 — MEDGENOME NEWS

ACTIA • CLARIA • PRIMA • MICRA • Business • Research • Awards • Genetic Counselling • Health Care

Affordability and accessibility of genetic tests still a challenge in India: Dr. Ramprasad, CEO, MedGenome Labs

Through both our diagnostics and research verticals we have built a complementary business model that allows us to gain a deeper understanding of many diseases, Dr. Ramprasad, CEO, MedGenome Labs told Financial Express.com.

Written by Sushmita Panda
December 24, 2022 10:00:00 am

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Vedam Ramprasad, Ph.D., Chief Executive Officer, India, MedGenome Labs. (FE.com)

Over the years, genomic sequencing and its analysis have become extremely important to identify inherited disorders, characterise the mutations that drive cancer progression, and tracking disease outbreaks.

In the years, several companies have forayed into this segment in order to "capitalise" on the diversity of the Indian population for predicting and controlling disease outbreaks.

FORTUNE exchange

MEDGENOME LABS LTD.
GENIUS IN GENETIC TESTING

Today, medicine is all about treating individuals by providing the right treatment to the right patient at the right time. With this vision, MedGenome was founded in 2013 to leverage the power of genomics and address the significant unmet need in the healthcare space. DR. VEDAM RAMPRASAD, CEO (India), MedGenome Labs Ltd. was instrumental in setting up the company's next generation sequencing (NGS) lab in Bengaluru, Karnataka which is the largest NGS lab in South Asia.

As CEO of the company, he has conscientiously built the diverse genetic testing portfolio aimed at constantly improvising and bringing new affordable tests to the market. He has been improving processes and optimizing utilization of resources making MedGenome the most trusted genomics brand among the clinician community.

DR. VEDAM RAMPRASAD,
CEO, MedGenome Labs Ltd.

MedGenome saw the need to create the market for genetic diagnostics at a time when sequencing-based genetic tests were not domestically available in India. Leveraging genomics to address several significant gaps in the healthcare space has therefore been the mission of the company, which offers over 1,300 tests covering all major key areas of genetic application. The company holds a large comprehensive genetic test portfolio in India that spans across five verticals namely Inherited diseases segment (Actia), Reproductive and Child Health (Claria), Cancer (Prima), Infectious diseases (Micra), and Consumer Wellness segment (Genessense). MedGenome's team has worked relentlessly since inception to create awareness, accessibility and affordability for these tests.

"Our bioinformatics platform enables us to develop new tests in-house efficiently and accurately based on strong research and market needs. The vast test portfolio across disease areas at affordable prices gives us a competitive edge. Over the years, we have introduced new tests that were important for the Indian market. With over a million children being born a year with genetic diseases that could not be diagnosed by other means, sequencing the genes to identify the cause was the only way to manage the disease better. In the prenatal space we introduced the first Indian Non-Invasive Prenatal testing (NIPT) to detect chromosomal abnormalities in the unborn child. Today, 96% of amniocentesis cases can be avoided through NIPT. We were the first company in India to provide this test validated by a pan India study," says Vedam Ramprasad, who has several peer-reviewed publications to his credit. He successfully built a strong genomics brand by focusing on science, optimizing resources, utilizing infrastructure efficiently, and ensuring quality. He simultaneously created awareness and educated physicians to influence the treatment landscape in key disease areas.

Recognised with several firsts in the Indian and Asian market, MedGenome has South Asia's largest NGS lab in Bengaluru, where a large Bioinformatics team is dedicatedly developing all the algorithms and tools in-house. "We have strengthened our logistics network to shorten the time taken for samples to reach our lab. Our latest high-end sequencing equipment, South Asia-specific baseline databases, and a strong team of bioinformaticians ensure quick turnaround and accurate reporting. We have an inhouse team of genome analysts to safeguard report quality. We also offer genetic counselling services for ease of interpretation of the reports and to resolve any queries from clinicians and patients. We continuously enhance our test menu to cater to the needs of the patients and clinicians," he explains.

"Our AI/ML enabled platforms and databases will continue to give us a strong edge and differentiated profile in this space. We are committed to maintaining our leadership position in the Indian genomics market and providing best-in-class research services across the globe. We plan to achieve this by increasing the accessibility and affordability of genomics in India and other emerging markets through deeper penetration, market consolidation, new product development, and bioinformatics solutions for remote diagnostic labs.," he says.

"Today, MedGenome's vision is backed by leading investors like Sequoia Capital, Sofina, HDFC, Leapfrog, IFC (World Bank), and Novo Holdings. Our core team has been with the company since its early days bound by a shared vision and commitment. This has also helped build a science and continuous learning focussed culture across the organization," he concludes.

BW Healthcare WORLD

Dr Amit Kakar Joins MedGenome As Board Of Directors

His experience also encompasses investing, operational and management roles across health-tech companies

MedGenome has announced the appointment of Dr. Amit Kakar, MD, from Novo Holdings to its Board of Directors. This announcement comes on the heels of MedGenome's USD 50 million funding round led by Novo Holdings in August 2022. They have also appointed Navjeewan Khosla, Principal, Novo Holdings, as a board observer.

Dr Kakar is a Senior Partner, Head of Novo Holdings Asia, and a healthcare professional with over 30 years of experience across key verticals, including medical technology, R&D, manufacturing, pharmacy retail, drug discovery,

livemint

MedGenome keeps $40 million for acquisitions this FY

Spotlight on genetic testing in inherited breast cancers

Inherited breast cancers are known to constitute about 10 percent of all cases of breast cancers

by Dr Ambreen Aman | November 9, 2022

SHARE

The incidence of breast cancer has been on the rise in India and the world over. It is the most common cancer reported in women, irrespective of their age and ethnicity, followed closely by cervical and ovarian cancer.

It is reported that breast cancer constitutes 13.5-14 percent of all cancers affecting women. In recent years, there have been more and more cases reported in younger women. About 0.5-1 percent of breast cancer cases occur in men.

Factors that Increase the Risk of Breast Cancer

Many factors increase the risk of breast cancer, of which female gender and age above 40 years are the most important. Other risk factors include younger age at menarche, older age at first childbirth, consumption of alcohol, obesity, exposure to harmful radiation, and a family history of breast cancer. Those with a positive family history may have mutations of certain genes known to cause inherited breast and ovarian cancer, the most significant of which are BRCA1 and BRCA2.

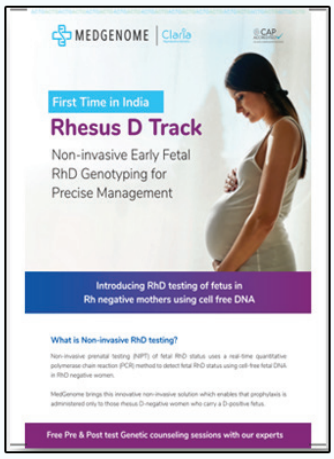
For press articles, please click https://diagnostics.medgenome.com/press/

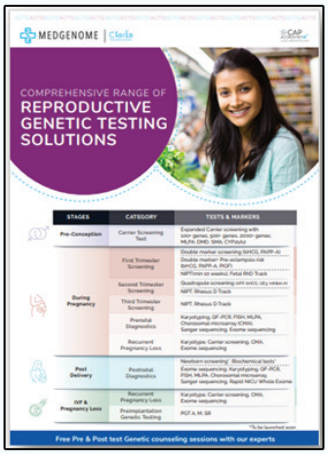
MedGenome Connect

Claria
Reproductive Genetics

Flyers – Rhesus D Track, Claria offerings, Carrier Screening Test, Maternal Markers

To create awareness about different offerings under Claria division





Claria Video

To create awareness about Claria offerings

Mailers – Recurrent Pregnancy Loss & NIPT Advanced

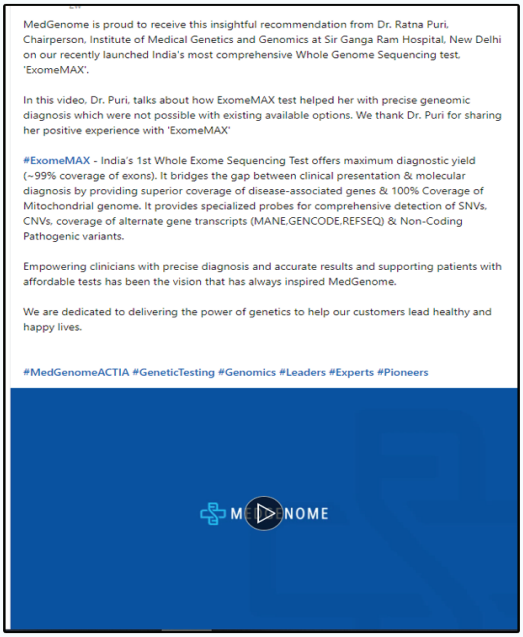
To reach out to maximum clinician for Claria offerings

Magazine Ad – Association of Obstetricians & Gynecologists of Delhi

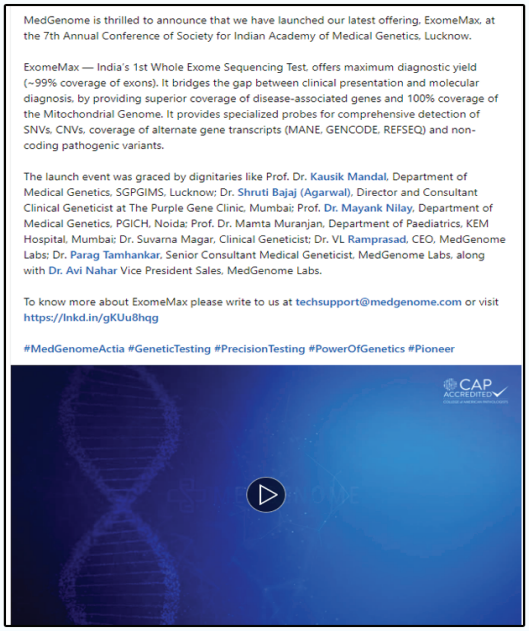
Magazine ad on Carrier Screening Test, Recurrent Pregnancy Loss, CMA
To create awareness about Claria offerings

We executed four dimensional activities across the product segment – brand awareness, sales support, clinician engagement, and patient education using both online and offline channels. Continued medical education was conducted by our expert scientific team across the product segment.

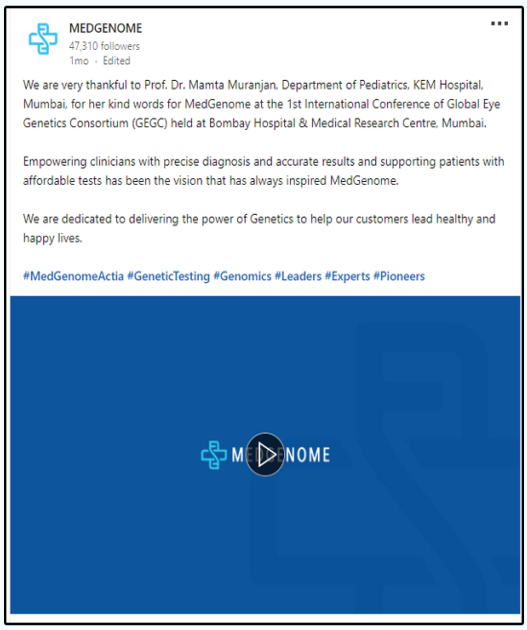
We had a formal launch of two of our tests "ExomeMAX" and "Comprehensive Ophthalmic Genetics" at a formal event in Lucknow and Mumbai respectively. Two of the leading clinicians gave their testimonials to our services as well.



Testimonial by Dr Ratna Puri



Launch of ExomeMax



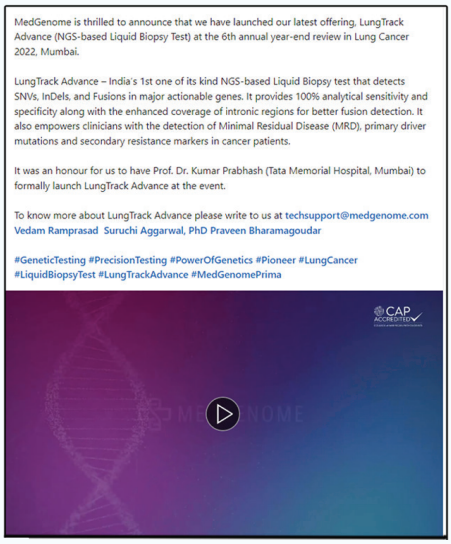
Testmonial by Dr Mamta

Opthal Launch pics

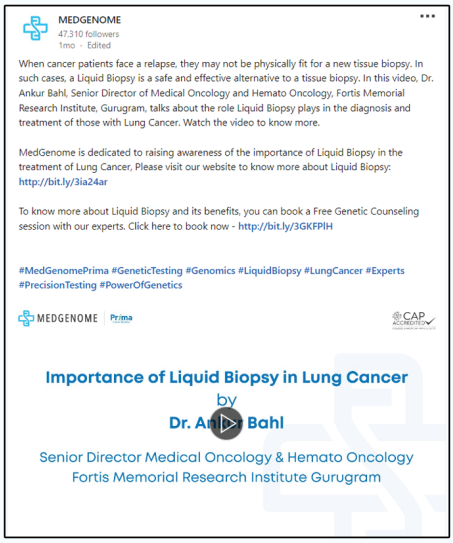
Our engagement with the leading hospitals/institutions/clinicians continued this quarter too, where our expert scientific team provided necessary updates and awareness about cancer genetics.

We had exhaustive campaigns focused on Breast Cancer, Lung Cancer, and Liquid Biopsy Test awareness. The campaign was targeted at both clinicians and the public. We conducted a patient education talk on breast cancer in association with BGS Gleneagles Global Hospitals where we engaged with more than 50 breast cancer survivors. We also spoke about early detection and management of lung cancer and breast cancer through activities such as doctors talk, educational animated videos and other activities through online and offline channels.

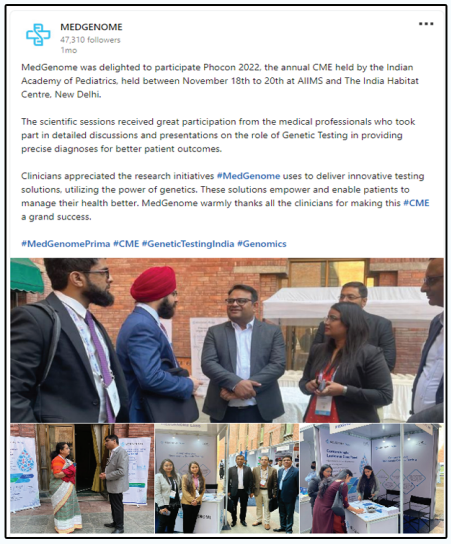
We launched LungTrack advance which is a liquid biopsy test for comprehensive analysis of SNVs, InDels and Fusions in Non-small cell lung cancer (NSCLC) patients.



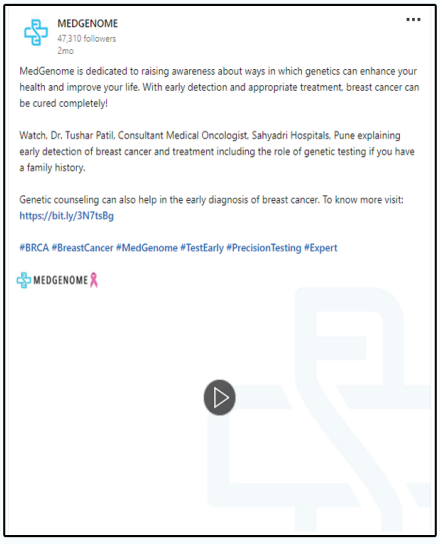
Launch of LungTrack Advance



Dr. Ankur Bahl, Senior Director of Medical Oncology and Hemato Oncology, Fortis Memorial Research Institute, Gurugram, talks about the role Liquid Biopsy plays in the diagnosis and treatment of those with Lung Cancer

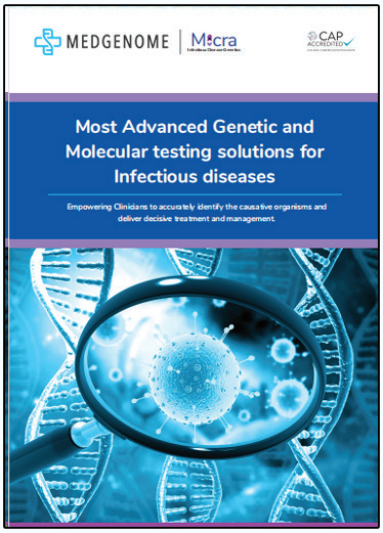


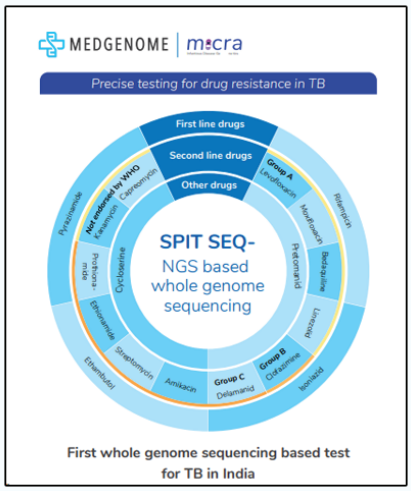
CME photo



Watch, Dr. Tushar Patil, Consultant Medical Oncologist, Sahyadri Hospitals, Pune explaining early detection of breast cancer and treatment including the role of genetic testing if you have a family history

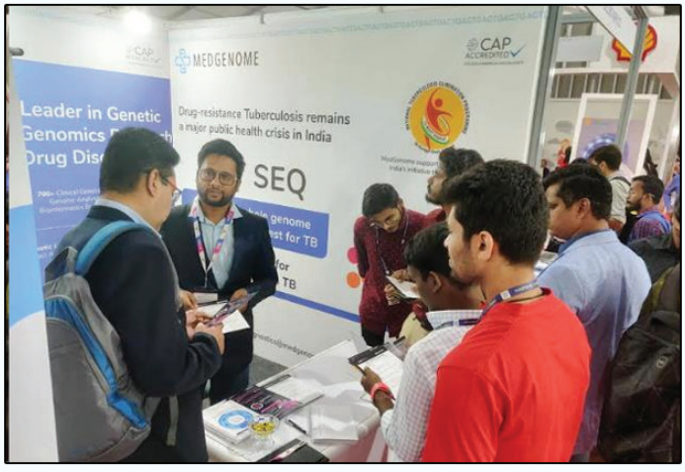
The last quarter was very encouraging and an active one too for Micra with a focus to engage more clinicians with CME, conference participation, Field work and test specific mailers and sales master training on Micra for sales support. The team is also working on a comprehensive Micra Brochure which contains in-depth information about all the tests along with tests launched through Micra.





SPIT SEQ- mailer and Social media post in November

Sales master training for Micra in November



Participation at Tech Summit, 2022 in November

GENESSENSE
Powered by MEDGENOME

We continued to evolve the various tests being offered under the Genessense portfolio in this quarter. We focussed on forging partnership with a few aggregators & conversations were initiated with some of the major players in this space. To ensure awareness about this brand, we also sent out emailers to our databases. The version 1 of the Kardiogen, Diabetes, Hypertension, Parkinson, Age-related macular degeneration (AMD) brochure and report were created, and the test was made available for internal testing with a prospective partner organisation.

Participation at Bengaluru Tech Summit, 2022 by MEDGENOME and Panel Discussion at Tech-Summit. MEDGENOME participated in the Panel discussion on "Genomics revolution 2.0 and its implications" at the Bengaluru Tech Summit, 2022.

Our CEO (India), Dr. Vedam Ramprasad shared insights about the future of genetics and its pertinent role in affordable healthcare, precise disease management and testing, population genomics and much more.

What's new

Research Publications

1. ***Genotype-phenotype correlation and natural history study of dysferlinopathy: a single-centre experience from India***

   Journal : Neurogenetics

   Click here for more

Tests launched

1. Minimal Residual Disease (MRD) by NGS in Solid Tumours (Liquid Biopsy)
2. Comprehensive Ophthalmic Genetic Disorder Panel
3. Rapid Exome Sequencing
4. LungTrack Advance-Liquid Biopsy test by NGS (SNV's, InDels & Fusions)
5. Endometrial Cancer panel by NGS
6. 1q gain/ 1p deletion by FISH for Multiple Myeloma

Proud moment

MedGenome awarded for
Global FT/IFC Transformational Business Awards 2022

- Transformational Human Capital Solutions.
- Overall Excellence in Transformational Business.

From Our US Office

MedGenome is a preferred partner for NGS and informatics expertise

2022 was an eventful year

Our journey in 2022 was focused on providing the utmost customer experience for the services and solutions that we delivered to you. Along with expanding our portfolio of services and solutions – the tissue dissociation and nuclei isolation services to support our single cell customers, streamlined antibody discovery using high-throughput single B cell receptor sequencing, TSO500 targeted panels for oncology research, single cell and bulk epigenetics assays. We improved our turn-around times on bulk transcriptomics, whole exome and whole genome projects by incorporating automation at multiple project stages and installing new sequencing capacity in 2022. Our sequencing team has delivered high-quality data consistently for a variety of library types throughout the year. We also rolled out a series of advanced and interactive analyses reports for each of our assays through our unique ManGo platform with novel data representations. This scale up on our bioinformatics capabilities is in line with our objective to support biologists and researchers to maximize the utility from genomic data.

We partnered with our customers to discuss the data and the subsequent analyses after each project is delivered to ensure that the results meet the researcher needs.

We built streamlined systems and communication processes for sample and data management with our customers, which allowed us to build transparency and a trusted relationship.

In 2023

We expect to continue to offer high quality support to your projects in 2023. We will be spending lab resources to optimize spatial transcriptomics and Hi-C assays in-house in 2023 to expand our services portfolio. With supporting bioinformatics analyses and tools to provide end-to-end service to our customers.

We will engage with customers on antibody discovery solutions and protein expression services given the highly experienced R&D talent that we have at MedGenome.

With growing sample volumes, we are committed to investing in our sequencing capacity even further in 2023 – to help us maintain the turn-around times (TAT) for the projects. We will discontinue our HiSeq X service by the end of this year.

We are also a preferred partner to customers who are looking to access South Asian genomic datasets in specific diseases areas (rare diseases, oncology, neuro-degenerative disorders, blood disorders, metabolic diseases) for discovery or genetic modifier studies. With a vast network of hospital collaborations in India, MedGenome is able to accelerate these studies with high impact.

Pandemic has tested our systems, processes and quality of team members beyond doubt. It has shown the importance of value added engagements with our customers that MedGenome strives for. Going into 2023, MedGenome is looking forward to continuing those relationships to advance genomics research by our customers.

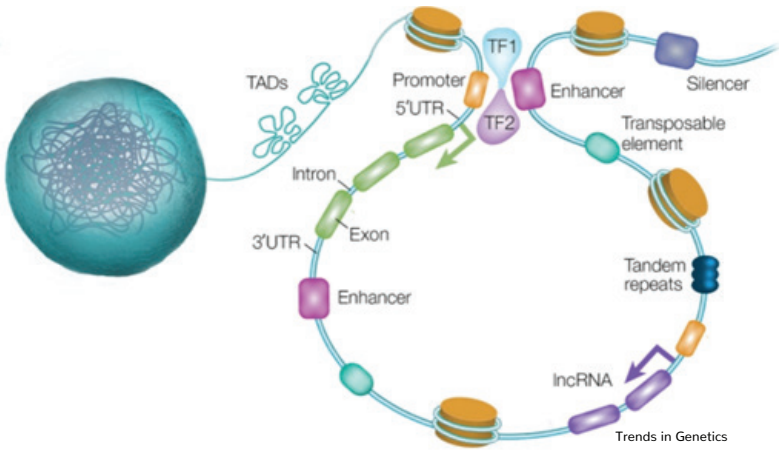
Sneak Peek into the World of Science

Genetic alterations in non-coding regions:
The hidden players in cancer genomics

Lakshmi Mahadevan, Ph.D
Principal Scientist

Cancer is a genetic disease caused by dysregulation of cell cycle progression and abnormal cell growth due to mutations present in cells. Since efficient management of this dreaded disease is dependent on the identification and functional characterization of cancer-causing mutations, significant efforts are being made, world over, towards the complete molecular characterization of the cancer genome. Advances in deep sequencing techniques like next generation sequencing in the recent years, have helped in revealing a plethora of causative mutations associated with cancer. However, our current understanding of the genomic landscape of cancer is largely limited to mutations affecting the exons and canonical splice sites.

Non-coding regions that can impact the disease genome



https://www.cell.com/trends/genetics/fulltext/S0168-9525%2820%2930172-4

A broad spectrum of molecular events are known to contribute to cancer development and progression. Genetic alterations including deletions, insertions, translocations, amplifications, missense, nonsense and frameshift mutations contribute to tumorigenesis by activating oncogenes or inactivating tumor suppressor genes. However, testing for cancer associated mutations in affected individuals / families often yield negative results.

Evidence from Genome Wide Association studies (GWAS) suggest that genetic variants in the non-coding but functional elements can be the key to the missing causes for various cancers. Mutations in non-coding regions, including aberrations in DNA regulatory elements, untranslated regions (UTRs), splice sites, non-coding RNA (ncRNA) along with synonymous mutations form the 'dark zone' of the cancer genome, which is mostly neglected in diagnostics. These are genetic aberrations that do not alter coding information but nevertheless contribute to cancer development by influencing gene expression or function through various mechanisms as described below.

Regulatory regions

Regulatory regions comprise of promoters and enhancers and mutations in these regions can either create or disrupt transcription factor binding sites, resulting in transcriptional up- or down-regulation of nearby coding genes. If oncogenes or tumor suppressor genes are affected, mutations in regulatory elements may lead to tumorigenesis. Further, promoter mutations, such as in the SDHD gene, are known to be associated with a shorter overall survival [1]. The most well characterized drivers of malignancy in regulatory regions are in the TERT promoter and have been identified in many cancer types [2].

5′ and 3′-Untranslated regions (5′-UTR and 3′-UTR)

The untranslated regions (UTRs) flanking the coding region in messenger RNA (mRNA) regulate protein translation and mRNA stability. Trans-acting RNA binding proteins (RBPs) and small RNAs bind to either simple sequence elements or secondary and tertiary structures in the 5′-UTR as well as the 3′ -UTR in order to mediate translational regulation. Variations in the UTR sequence may reduce translation efficiency by impairing accessibility for the translational machinery.

Upstream open reading frames (uORFs) in the 5′UTR region can impair translation from the original open reading frame (ORF) or induce mRNA decay. A common polymorphism in the 5′ -UTR of the ERCC5 gene leads to the expression of a uORF, the translation of which induces the expression of ERCC5 protein leading to resistance to platinum-based chemotherapy and decreased survival in pediatric ependymoma [3]. Alternatively, mutations within the 5′ -UTR can create aberrant initiation codons.

As in the 5′-UTR, elements in the 3′ -UTR can also regulate translation and mRNA stability by alternative cleavage, aberrant splicing and de-adenylation. For example, a mutation that creates a premature polyadenylation signal in CCND1 gene shortens its 3′-UTR and increases the risk of mantle cell lymphoma [4].

Intronic variants

The majority of characterized intronic splicing mutations affect the canonical splice sites. However, splice site modifications are also caused by mutations outside the consensus GT-AG splice site. These mutations can give rise to cryptic splice sites, which in turn result in alternative splicing, leading to deletion of the adjacent exon or retention of the adjacent intron in the processed mRNA transcript. In addition to alternative splicing, mis-splicing events, which introduce premature termination codons in abnormally spliced transcripts and elicit mRNA degradation via nonsense-mediated decay, have also been described [5].

Non-coding RNAs (ncRNAs)

Non-coding RNAs are a class of transcripts with low protein coding potential, involved in diverse cellular processes including cell cycle regulation, differentiation and apoptosis and can therefore act as tumor suppressors or oncogenes. Ranging from abundant and functionally important types like transfer RNAs (tRNAs) and ribosomal RNAs (rRNAs) to small RNAs such as microRNAs, siRNAs, piRNAs, snoRNAs, snRNAs, exRNAs, scaRNAs and the long ncRNAs, non-coding RNAs are widely expressed and have key roles in gene regulation. NcRNAs that have recently emerged as relevant to cancer include microRNAs (miRNAs) and long non-coding RNAs (lncRNAs), which alter the stability and translation of cytoplasmic mRNAs and interfere with signaling pathways.

Synonymous mutations

Unlike non-coding variants, synonymous mutations occur in the coding region of a gene but do not alter the amino acid sequence. Hence, this category of mutations are also generally considered harmless. In cancer, synonymous mutations are estimated to account for 20% of all point mutations, 6 to 8% of which may act as driver mutations [6]. These variations can cause splicing errors by disruption or creation of splicing regulatory sites, inactivation of existing splice sites and activation of cryptic splice sites, leading to exon skipping and protein truncation. They could also lead to alterations of mRNA structure and stability, gain or loss of miRNA binding sites and changes in translation efficiency. When a synonymous substitution results in a rare codon, transfer RNA (tRNA) (un)availability can decrease the translational speed, which can lead to changes in protein folding and conformation.

To conclude...

In the recent years, the emergence of targeted therapies has revolutionized the treatment of cancer. A detailed understanding of the mutational heterogeneity in tumors can have tremendous impact on the survival of patients. So far, cancer research has mainly focused on mutations that alter the protein-coding fraction which represents only less than 2% of the human genome. Variations present in the non-coding genomic sequences, which can also serve as potential therapeutic targets or novel biomarkers, are yet to be brought to light.

The advent of high-throughput deep sequencing techniques has led to rapid advances in the field of cancer genomics by enabling sequencing of a large number of complete cancer genomes. However, in addition to generation of massive data, in-depth analyses of the non-coding sequences to identify mutations of functional impact are required.

Genetic tests tailored to capture and interpret the effect of such non-coding/silent variations are the need of the hour, as they can significantly improve the clinical outcome of cancer patients. Thus, considering the potential impacts on cancer diagnosis, prognosis, treatment response prediction and selective targeting as a therapeutic strategy, comprehensive research focusing on the detection, mechanisms and impact of non-coding and silent mutations in cancer will be of utmost importance in the future.

Examples of non-coding and synonymous variants in cancer
(data compiled from Diederichs et al, 2016)

GENETIC EVENT	EFFECT ON GENE REGULATION/ PROTEIN	GENE	CANCER	ALTERATION
MUTATIONS WITHIN REGULATORY DNA ELEMENTS				
New binding site for activating transcription factor	Upregulation	TERT	Medulloblastoma, Hepatocellular carcinoma, Urothelial carcinoma, Melanoma, Glioblastoma	C228T, C250T (promoter)
		TAL1	T-cell acute lymphoblastic leukemia	insertion (super-enhancer)
		MCL1	Chronic Lymphocytic Leukemia	insertion (promoter)
		CCND1	Renal cancer	multiple SNPs (enhancer)
		MMP1	Breast cancer	(—1,607) 1G/2G (promoter)
		LMO1	Neuroblastoma	SNP in super -enhancer
New binding site for repressing transcription factor	Downregulation	BRM	Hepatocellular carcinoma, upper digestive tract cancer, non-small cell lung carcinoma	insertion (—741, —1,321)
Disrupted binding site for activating transcription factor	Downregulation	SDHD	Melanoma	3 hotspots C > T (promoter)
		WDR74	Multiple	52 hotspots C > T (promoter)
		PAX5	Chronic lymphocytic leukemia	multiple mutations (enhancer)
		CK-19	NSCLC, gastric cancer	G (—99)C (promoter)
Disrupted binding site for repressing transcription factor	Upregulation	AMACR	Prostate cancer	germline deletion (promoter)
Unknown	Downregulation	PLEKHS1	Multiple	23 hotspots C > T (promoter)
		CASP8	Gastric cancer	—652 6N del (promoter)
		BRCA1	Breast/ovarian	5-kb deletion (promoter)
MUTATIONS IN 5'UTR				
Upstream ORF (uORF)	Decrease	CDKN1B	Multiple Endocrine Neoplasia	4-bp deletion C.-456-453del (germline)
Aberrant initiation codon	Decrease/no protein	CDKN2A	Melanoma	G-34T (germline)
Internal ribosome entry site (IRES)	Increase	C-MYC	Multiple myeloma	C2756T
Upstream ORF (uORF)	Increase	ERCC5	Pediatric ependymoma	A25G
Splice site/secondary structure	Decrease	RAD51	Breast cancer	G135C
Secondary structure	Decrease	RB1	Retinoblastoma	G17C, G18U (SNV, N/A)
Internal ribosome entry site (IRES)	Decrease	TP53	Melanoma	C119T (SNP)

MUTATIONS IN 3'UTR				
Premature polyadenylation	Increase by enhanced stability of truncated mRNA	CCND1	Mantle cell lymphoma	Several genomic deletions in 3'-UTR
Decreased efficiency of polyadenylation	Decrease	MSH6	Lynch syndrome	Duplication of 20 bp close to the polyadenylation site
Change within polyadenylation signal	Decrease	TP53	Cutaneous basal cell carcinoma, prostate cancer, colorectal adenoma, glioma	rs78378222 A/C
APA	Increase by enhanced stability of truncated mRNA due to miR-binding site loss	PSMD8, TM9SF3 CD59, ANKH CIAO1, SRSF5, MRSP16 NDUFA6	Small intestinal neuroendocrine tumor	NA
INTRONIC MUTATIONS AFFECTING SPLICING				
Cryptic splice donor site	Partial intron retention	ATM	Breast cancer	IVS28-159A>G
Cryptic splice donor site	Partial intron retention	BRCA1	Breast/ovarian cancer	IVS16+6T
Polypyrimidine tract affected	Exon 5 skipping	BRCA2	Breast/ovarian cancer	IVS4-12del5
Cryptic splice donor site	Retention of a cryptic exon	BRCA2	Breast/ovarian cancer	c.6937+594T>G
Creation of a de novo splice site	Partial intron retention	BUB1B	Gastrointestinal neoplasia	c.2386-11A>G
Splice donor site	Creation of new splice donor site	CDKN2A	Melanoma	IVS2-105 A>G
Cryptic splice site	Inclusion of a cryptic exon	CDKN2A	Melanoma	IVS1+37 G>C
Splice acceptor site	Intron retention	MEN1	Multiple endocrine neoplasia type 1 (MEN1) and related disorders	894-9 G>A
Creation of a novel splice acceptor site	Inclusion of eight additional nucleotides	MEN1	Multiple endocrine neoplasia type 1 (MEN1) and related disorders	IVS9-9 C>G
Splice acceptor site	Exon 2 skipping	MLH1	Colon cancer	IVS1-11T>A
Splice donor site	Inclusion of a cryptic exon	MSH2	Colon cancer	IVS1-478
Splice donor site	Exon 6 skipping	PTEN	Juvenile polyposis syndrome	IVS7+7A>G
Cryptic splice donor site	Partial intron retention	RB1	Retinoblastoma	IVS23-1398A>G
Polypyrimidine tract of a splice acceptor site	Exon 9 skipping	RB1	Retinoblastoma	IVS8-10T>C

SYNOMYMOUS MUTATIONS				
Splicing	Exon skipping	BRCA1/2	Breast/Ovarian	BRCA1, 3719 , G > T; BCRA2, 744 G > A; BCRA1, 231 G >germline)
	Exon skipping, New splice site	APC	Adenomatous polyposis	1869 G > T (germline) 5883 G > A
microRNA binding	Loss of has-miR-671-5p binding site	BCL2L12	Melanoma	51 C > T
Translation/ Protein folding	Rare codon might lead to changes in cotranslational folding	MDR1	Multiple drug resistance	3435 C > T

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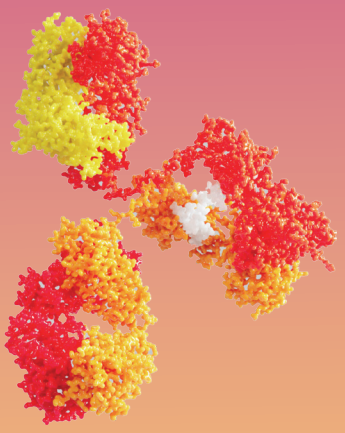
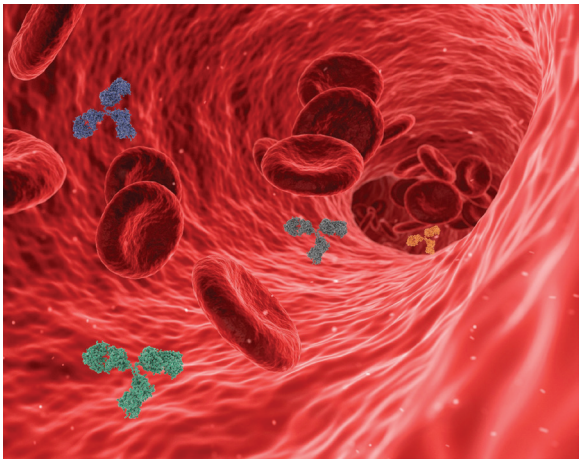
Sneak Peek into the World of Science

Immune Risk Profiling for Anti-drug Antibodies following treatment with Monoclonal Antibody-based therapeutics



Savita Jayaram, Ph.D
Senior Bioinformatics Scientist

Introduction



Advances in antibody engineering and its high specificity have driven rapid development and production of fully human Monoclonal Antibodies (MAbs) hailed as wonder drugs with long lasting remissions. They have evolved as the predominant treatment modality for several diseases, including autoimmunity, infectious diseases and cancer. However, undesirable immune responses that target the MAbs can lead to subsequent therapy failure, or worse can cross-react to endogenous proteins, leading to even fatal consequences. These therapeutic proteins are usually well-preserved *ex vivo* but may be physically altered *in vivo* with substantial impact on immunogenicity. Immunogenicity is a significant concern for therapeutic protein products in preclinical development as it has the potential to affect product safety, and efficacy. Drug immunogenicity manifests as anti-drug antibodies (ADAs) and some of these MAbs can show immunogenicity of up to 70-85%.[1] For example, Alemtuzumab, and anti-CD52 immunomodulator, used to treat multiple sclerosis, induces ADAs in 85% of the patients, of which majority are neutralizing ADAs. [2] Over 90% of the currently approved MAbs cause immunogenicity. Detection of ADAs can present unique challenges as both the drug and the analyte are antibodies, and they can alter the drugs pharmacokinetic (PK) or pharmacodynamic (PD) properties influencing drug's efficacy. Further, they can neutralize the drugs therapeutic effects and/or cause severe adverse reactions in patients.

There is an immediate need to predict the propensity of the drug to generate ADAs and evaluate the inherent risk before the drug hits the market. The consequences of immunogenicity are highly variable and idiosyncratic, ranging from no evidence of clinical effect to severe allergic or anaphylactic reactions, often leading to a reduction in efficacy, or induction of autoimmunity. Detection and analysis of ADA formation is not only helpful to understand the immunogenicity risk but also to circumvent its harmful effects through antibody engineering. The work could have significant impact on the field of designing protein therapeutics, where immunogenicity is a serious liability.

The discovery and development of MAbs have seen considerable advancement with quicker and more efficient therapies.[3] Since the advent of the first MAb, in 1986, the number of antibody therapeutics have steadily increased with the 100th MAb drug being approved by FDA in May 2021.

Figure 1: shows the number of antibody therapeutics granted approval in US since 1997. Currently, of all the MAbs, 54% are fully "human" in origin, 32% are "humanized" containing murine CDRs in the fragment antigen binding (Fab) domains by CDR grafting and 14% are "chimeric" containing murine variable regions where only the fragment constant (Fc) region is replaced by human sequences. In general, humanized MAbs are those in which small but critical parts of the complementarity-determining region (CDR) are from non-human sources, but the larger constant regions of the immunoglobulin heavy and light chains are human-derived. Chimeric antibodies are generally those in which the Fc part of the immunoglobulin molecule (but not the CDR) is of a human sequence. In general, chimeric MAbs and humanized antibodies contain >65 and >90 percent human sequence, respectively.[4] Induction of ADAs was initially ascribed to murine origin that are seen as 'non-self' by our immune system, but ADAs are also induced by fully human MAbs, so there may be other factors at play, some of which are discussed below.

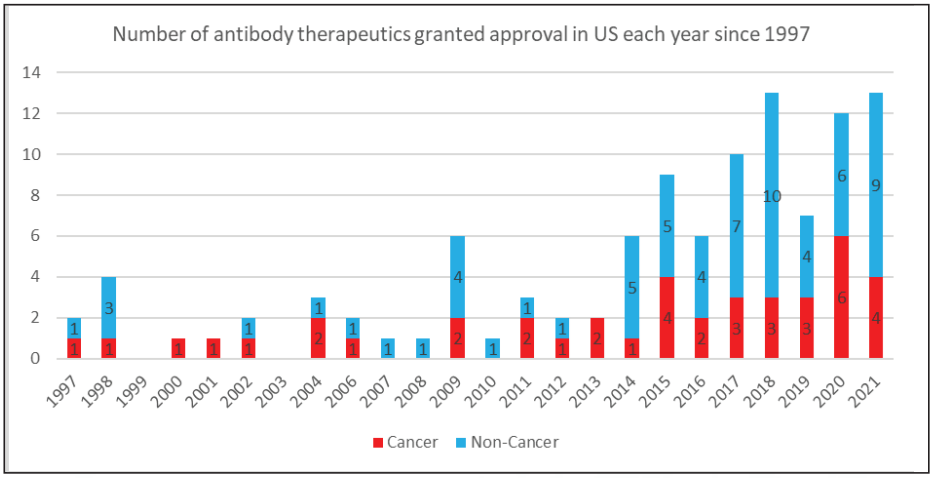


Figure 2: Therapeutic monoclonal antibodies approved by FDA from 1997. MAb data was obtained from The Antibody Society website https://www.antibodysociety.org/antibody-therapeutics-product-data/, and sorted for cancer (red) and non-cancer (blue) use.

Molecular Mechanisms leading to ADA induction by MAbs

Accurate ADA detection is essential to provide clinicians with the necessary information for patient monitoring and timely clinical intervention. The Food and Drug Administration (FDA) has outlined detailed recommendations for the adoption of a risk-based approach to evaluating and mitigating immune responses or adverse reactions associated with therapeutic protein products that affect their safety and efficacy.[4] While some of these contributing factors are well known, the molecular mechanisms of how therapeutic MAbs elicit ADAs is still not completely clear.

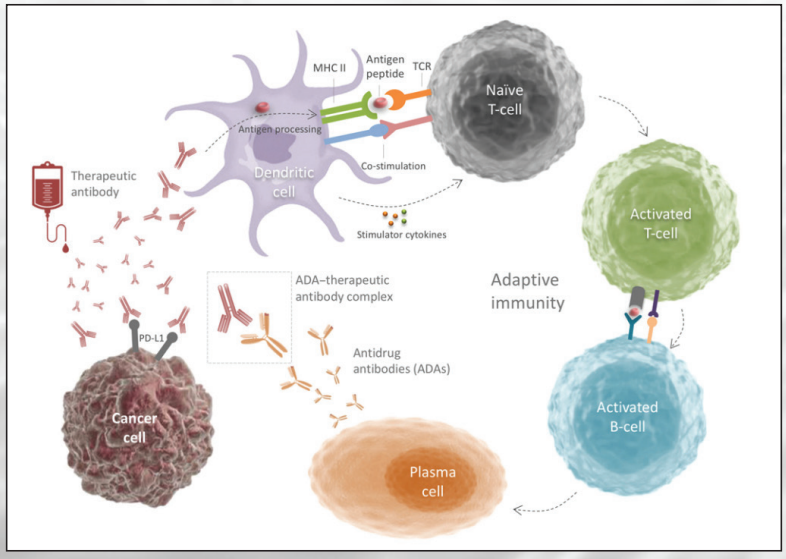


Figure 2: Schematic showing the possible mechanism of ADA induction (Figure from Ref 5) The MAbs can act as antigens and be internalized, processed and presented by antigen presenting cells (APCs) to T-cell receptors (TCRs) in the context of MHC class II molecules. Some of the peptides that appear sufficiently different from self, could trigger a T cell response. Once activated, in the T-cell dependent pathway, the T-helper cell, depending on the cytokine milieu, differentiates into Th1 and Th2 cells, that can in turn activate the B cells to differentiate into ADA-producing plasma cells (shown as a schematic in Figure 2). Alternately, in a T-cell independent pathway, multiple epitopes can crosslink the B cell receptors (BCRs) transforming B cells into plasma cells producing ADA.

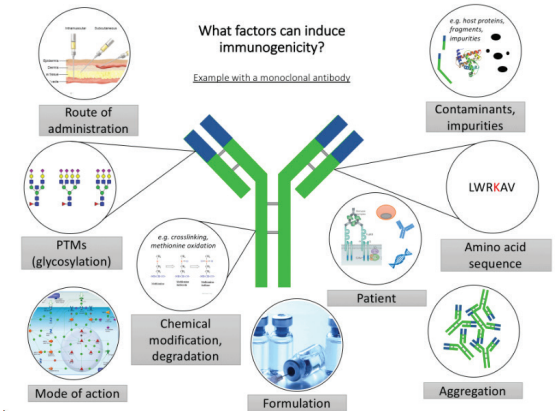


Figure 3: Factors influencing immunogenicity.
(Source: https://hartmannwillner.com/need-know-immunogenicity/)

Several patient and drug related factors can influence ADA formation such as patients genetic status, drug dosage, impurities in the formulation, structural features such as amino acid variations, glycosylation, Ag-Ab aggregates and so on.[1] Frequently, MAbs cross reacts to or inhibits a non-redundant endogenous protein. For instance, Alemtuzumab's high frequency of ADA induction may be related to CD52 expression patterns.[2] Enhanced product aggregation or binding outside the antigen binding site can influence efficacy. Altered antigen processing and presentation can occur due to genetic factors, compromised immunological status or competence of the patient. This may lead to the generation of novel 'non-human' peptides, triggered by prior sensitization or a history of allergies. Enhanced HLA binding of MAb-related peptides can occur, for instance, deamidated and citrullinated proteins generated peptides with enhanced class II binding. The disease state can also influence immunogenicity. For instance, rheumatoid arthritis patients have a higher likelihood of developing ADAs towards a MAb drug than spondylarthritis. Hyper inflammatory state, such as the cytokine storms seen in COVID19, can significantly increase the risk of immunogenicity of a therapeutic protein product. Sometimes impurities such as aggregates and residual DNA or proteins introduced during MAb formulation or in the MAb expression system may have adjuvant activity and can influence drug immunogenicity. Additionally, higher MAb doses are found to be associated with higher ADA particularly affected by dosing frequency, concentration and mode of administration. Subcutaneous, intradermal, and inhalational routes of administration were associated with increased immunogenicity compared to intravenous (IV) and intramuscular routes. PTMs such as glycosylation or pegylation of proteins may elicit immunogenicity. Changes in Fc glycosylation may also affect ADA induction. For instance, removal of N-linked glycosylation of the Fc domain was shown to reduce immunogenicity. These factors are concisely depicted in the schematic in Figure 3.

Generating Immunogenic peptides using OncopeptVAC™

MedGenome developed a novel proprietary and now patented (US10350280) algorithm, OncoPeptVAC™ to accelerate identification of cancer vaccine candidates.[6] This pipeline was successfully validated in two different in-house studies. Three mutant peptide antigens were selected from Lynch syndrome-colorectal cancer patients following neoepitope prioritization using OncoPeptVAC™ pipeline, and shown to induce a potent CD8 T cell response.[7] In another recent study, immunodominant T-cell epitopes of SARS-CoV-2 spike antigens showed robust pre-existing T-cell immunity in unexposed individuals, contributed by TCRs that recognize common viral antigens such as influenza and CMV.[8] Interestingly, these viral epitopes lacked sequence identity to the SARS-CoV-2 epitopes. Both studies were published in Nature, Scientific Reports. Further ongoing studies from MedGenome showed the effects of peptide length and peptide dosage on CD8 T-cell activation. The immune response of a 9mer or 15mer version of HLA-2-restricted 'GILGFVFTL' epitope was compared to determine which made a better vaccine candidate, by measuring the CDR3 expansion as a measure of T-cell epitope engagement diversity.[9] It was seen that the 15mer epitope produced a more robust and sustained response, and private CDR3s not expanded by 9mer peptides. All these studies, show the potential utility of our pipeline in accurately predicting prototypical immunodominant vaccine candidates that can be further screened using our proprietary OncoPeptSCRN™ T-cell assay platform.

The same OncoPeptVAC™ pipeline can correspondingly be used to identify immunogenicity risks and ADAs in antibody-based therapeutics. Particular regions within the MAb sequences such as the CDR or FW regions may be highly immunogenic, especially if they represent the chimeric part of the protein and will have an over representation of immunogenic peptides. The workflow depicted in Figure 4 incorporates both Class-I and Class-II restricted immunogenic peptides with their corresponding immunogenicity scores and percentile ranks generated using OncoPeptVAC™. The peptides are then prioritized using thresholds for 'Immunogenicity Score' > 0.2 and 'Percentile Rank' < 0.8 for Class I peptides and 'Percentile Rank' > 5 for Class II peptides. Further prioritization for Class I peptides can be done using what we call a 'Prioritization score' > 1.5. The HLA allele frequencies in the world-wide population was then added for the resulting HLA alleles from http://www.allelefrequencies.net/.

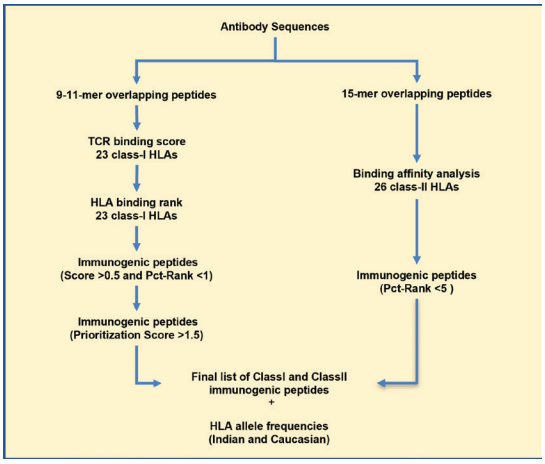


Figure 4: Workflow for generating immunogenic peptides

Distribution of Immunogenic Peptides per HLA type

Some human leukocyte antigen (HLA) haplotypes of the patients can be potentially used as biomarkers to predict vulnerable patients and may play an important role in prevention of ADA responses.[10] HLA polymorphisms in HLA-DRβ-11, HLA-DQ-03, and HLA-DQ-05 alleles, HLADQA1 05 (A > G) were shown to influence ADA formation.[1] Some HLA haplotypes may also predispose patients to develop unwanted antibody responses to specific products. HLA mapping studies, in such cases, can identify a subset of patients at an increased risk. Further, certain immunogenic peptides appear to have an increased preference for particular HLA haplotypes.[4] This can be inferred by looking at the HLA propensities of the immunogenic peptides and their relative frequencies in the population.

Discussion

The immunogenicity of MAbs is complex and there are a number of often poorly understood factors which makes it difficult to predict with any certainty whether a therapeutic or diagnostic monoclonal antibody is likely to provoke a clinically relevant immune response. Potential adverse effects of immunogenicity include infusion reactions and reduced efficacy, although these are not easily predicted. *In vitro* non-clinical approaches aimed at identifying T-cell epitopes have been developed but these have limited capacity to predict immunogenicity of a therapeutic protein in humans. However, *in silico* methods such as OncopeptVAC™ can be useful for assessing the risk and shortlisting the immunogenic epitopes, which can then be followed by further experimental immunogenicity testing. Monoclonal antibody drugs need to go through extensive testing before reaching the clinic and several often fail in various stages of drug development. Currently, more than 570 MAbs are in clinical trials, of which about 90% are in early stage studies being assessed for safety or efficacy in patient cohorts.[11] Tests done on non-human primates produce significant anti-CDR and anti-framework responses against human or humanized MAbs, which may closely mimic human responses and may be an appropriate positive control. However, non-primate species usually produce antibodies primarily against the constant regions of the MAb, which is unlike human responses.

The next generation of antibody therapeutics are the VH or VHH antibodies constituting the antigen binding fragment/variable domain of heavy chain only antibodies, also referred as Nanobodies. Heavy chain only antibodies are produced naturally by camelids and sharks. These have gained considerable attention due to their high binding affinity, modular properties, cost-effective manufacturing and attractive small size enabling penetration into solid tumors. For example, Caplacizumab that is used for treatment of a rare blood disorder, aTTP. However, their use is hindered by the presence of anti VH(H)pre-existing ADAs or anti-hinge antibodies, observed in nearly 50-60% of drug-naive healthy individuals.[12] Recent studies suggest structure based methods to abrogate pre-existing immunogenicity-related liabilities by adding 2 proline residues at the VHH C-terminus.[13] Broadly, antibody biotherapeutics can be made safer by identifying modifications capable of reducing pre-existing ADA binding.

In conclusion, this approach addresses the critical need to provide suitable risk profiling strategies to identify the propensity of MAbs to generate immunogenic T cell epitopes using *in-silico* approaches, to reduce the inherent risk of immunogenicity and identify the regions that can be re-engineered for mitigating this risk. Further, it would reduce the time taken for experimental evaluation of treatment-emergent ADA neoepitopes for protein biotherapeutics.

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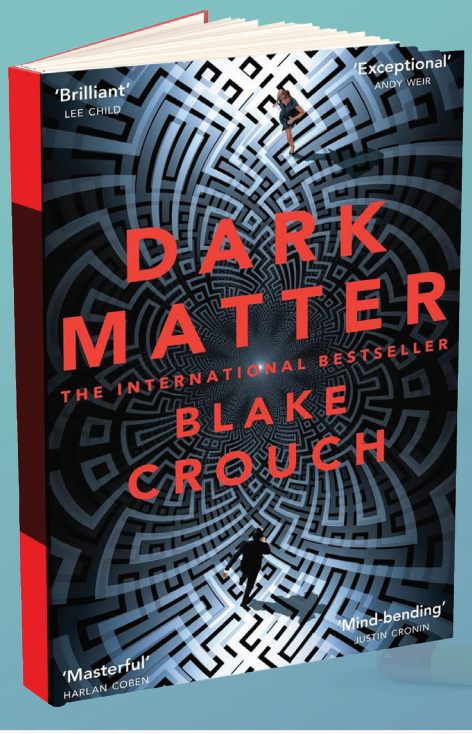
Book Review



Book

DARK MATTER

Book review by

Shalmali Sardesai
Consultant, Corporate

Are you happy in your life?

"What if?" - We all have had this question about looking at our life differently. What if you had not chosen your current path? What if you had just made different choices at different points in time? Each of those different choices could have branched out onto a different path with a different you.

Now imagine all those different worlds existing at the same time! Every possbility that could ever exist, does exist in its own universe - The possibility of alternative realities!

What if you could live all those paths wished but not taken? This is the premise of Blake Crouch's Dark Matter.

Dark matter is called "dark" because it is difficult to detect. Life has similar layers which are often hidden from our view.
Set in Chicago, the story revolves around Jason Dessen, an ordinary physics professor who lives with his wife, Daniela and their teenage son, Charlie. One evening, he and Daniela are reflecting on how their lives could have been different if they had pursued their professions, in physics and painting, respectively, more passionately, instead of being together and starting a family although they seem to be happy with their choices. Little does he know that he is going to live all those what ifs simultaneously as he becomes a part of the multiverse in which various versions of his world exist simultaneously and thus become a part of a thrilling and dangerous adventure in the process.

"The Many-Worlds interpretation of quantum mechanics posits that all possible realities exist. That everything which has the probability of happening is happening. Everything that might have occurred in our past did occur, only in another universe".

The book explores the concept of parallel universe where a universe exists alongside another universe with each having the same characters living in different circumstances. A version of Jason somewhere in the multiverse has created a giant cube with the ability to put a person in a state of simultaneously observing all possible realities at once. This, in turn, allows the person in the cube, with the right drugs, to choose between other realities and then see how different life would be if that were the reality he had chosen to live. The story unravels Jason's fight against multiple other Jason's from the different worlds, to choose his current life and be able to reunite with his family.

Although the book is based on the theory of quantum mechanics, the physics concepts are kept simple and woven into Jason's experiences which makes it easy for the reader to imagine being in Jason's shoes. Science is made adventurous and thrilling with all the twists and turns and at every point it makes the reader want the original Jason to return to his world.
Our personal decisions and the choices made, not made, the paths chosen, not chosen at various points in our lives, ultimately affect our lives, the lives of those around us and our world but are the chosen paths meant to be?
You create your world! The real question is "Are you happy in your life?"

From our Colleagues

Art meets Science

The most beautiful thing we can experience is the mysterious.
It is the source of all true art and science.
— Albert Einstein

By:
Raksha Patel
Business Development Executive

From our Colleagues

Our employee's little Picasso :)

By
Likhitha G (11 Years)
DNA of Girisha D C,
Zonal Sales Manager

From our Colleagues

By
Soumyadipta Das
Genome Analyst Trainee

Employee Connect

Our New-Joiners


A N Amrutha Sindhu


Abhishek


Aishwarya Prashant Pargaonkar


Amritha K S


Ananthi


Aniket Mahadeo Motghare


Anisha Tomy


Ankeet

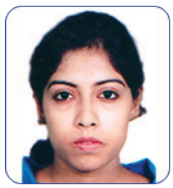

Ankita Ambig


Anupriya


Anuradha Srinivasan


Anusha


Arshad Iqbal


Arunima Ghosh


Ashvinee Kumar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C Karolin Lice


Deepak Dixit


Deepika G S


Deepthi Udupi


Divin A Wilson


G Chethana Ganga


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Gangotri Patra


Gaurav Kumar


Geetharaj J A


Hathim A S


Hirak Jyoti Kalita


Hriddhi


Ishani Deepakbhai Joshi


Jayalakshmi T R


Jayanth Narasu


Jeyaram Balaguru


Jincy Mariam Jose


Jugnu Kumar


Jyoti Raj Anand


Kalyani K


Kanakaraju Ganesetty


Kapil Chandrashekhar Chindarkar


karan Singh


Karthik Manjunath Guddadamane


Kartik Varshney


Kotamraju Venkata Pavan Kumar


L Yashaswini


Lakshmi Raj


M Ajith


Mahammad Jawed Akhtar


Mahanthesh CV


Mahesh S


Mahima R


Malobi Nandi


Manju N


Manoj Kumar A


Mohd Arif Khan


N Naveen Raj


Nagesh Mallesham Maheshuni


Nancy Priya


Neeraja S


Neethu Divakaran


Nidhi Dongre


Nivedha


Nutheti Sivaranjani


Oommen K Mathew


P I Megha Vinod


Pooja S Madhavan


Poojaraj Pushparaj Pandaradathil


Prajapati Yash Vashrambhai


Pranjali Bibhishan Thorat


Preethiba Gopi


R Suresh Naik


R. Meera


Raj Shingala

Rajkumar Arumugam

Raju Kumar Gupta

Rajupalepu Veera Venkata Lakshmi Narayana Pavan Phani

Raksha Dilip Patel

Ramani Balasubramanian Vasantha

Ramya T

Rishi Ranjan Gupta

Rumana Tasneem


Rupam Tamrakar


S Bhavyashree


S Pavitraa


Saiman Raj S


Sakshi Govind Sharma


Sandeep Kumar


Sandhya M


Sanjib Kumar Das


Saroja Daniel


Sella Vamsidhar reddy


Shadakshari A N


Shajitha


Shashidhar P


Shivakumar V


Shivanee Gupta


Sneha Ghosh


Sourav Sarkar


Srijith V M


Srikanth Gowda R


Sunil Kumar C


Sushma M


Tajuddin Baidya


Tanya Shree


Tarigonda Nandan Kumar


Thasmiya A Hadimani


Trina Mondal


Tsewang Tsamchoe


Vaghela Mukeshkumar Ganeshbhai


Vaibhav Lawoo


Vaibhav Prakash Wagh


Varsha


Varun S


Vijil V V


Vishnu Prasad N P


Yashwanth Ram D R

Photo Feature

Christmas Celebrations

We said good bye to Year 2022 with celebrations, Joy of giving and other fun filled activities. Below are some glimpses of the celebrations.

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