

War against infections



Table of Contents

FOREWORD	5
ZAWER BHUJWALA	
FROM THE EDITORIAL DESK	7
JYOTSNA RAO & UMA MAHESWARI KRISHNAN	
ABOUT US	8
UMA MAHESWARI KRISHNAN	
JOIN MISI	9
MEMBERSHIP FORM AND DETAILS	
IMAGING INFECTIOUS DISEASES – A CLINICIAN'S PERSPECTIVE	10
DR. VENKAT RAMESH, DR. SUNEETHA NARREDDY	
MOLECULAR IMAGING IN INFECTIOUS DISEASES: A PRECLINICAL PERSPECTIVE	14
SHRIDHAR NARAYANAN & VIDYA SHRIDHAR	
IMAGING STOCHASTIC GENE EXPRESSION OF HIV-1	18
SRESHTHA PAL, VIJETA JAISWAL, UDAYKUMAR RANGA	
COVID-19- A WAKE-UP CALL FOR INFECTIOUS DISEASES IMAGING	21
GAYATRI GOWRISANKAR	
RADIOLOGY OF COVID-19: THE BASICS	24
RON KORN	
ROLE OF ARTIFICIAL INTELLIGENCE IN INFECTIOUS DISEASES	27
R.ELAKKIYA	
MRI FOR IMAGING INFECTIOUS DISEASES	30
K. SUDHEER	
PHOTOACOUSTIC MOLECULAR IMAGING OF INFECTIOUS DISEASES	33
RAJSEKHAR KOTHAPALLI	
UPCOMING EVENT	37
WEBINARS	

KNOW THIS TECHNIQUE - FISH	38
MAMATHA CHIVUKULA	
SPOTLIGHT MEMBER	40
M.G.R. RAJAN	
YOUNG PROFESSIONAL COLUMN: IMAGING - A TORCH IN THE DARK	41
SAKTHIVEL GANDHI	
COVID-19 DIAGNOSIS & TREATMENT: WHERE DO WE STAND?	44
UMA MAHESWARI KRISHNAN	
FOCUS INTERVIEW: DR. MURALI KRISHNA CHERUKURI	46
MURALI KRISHNA CHERUKURI, NATIONAL CANCER INSTITUTE, USA	
PRODUCT REVIEW: MULTI-PHOTON LASER SCANNING MICROSCOPE	48
J. SEBASTIAN RAJA & GANESH KADASOOR	
IMAGE OF THE QUARTER	52
J. SEBASTIAN RAJA	
OPINION: AI IN INFECTIOUS DISEASE: PROMISE OR HYPE?	53
DEEPAK BEHERA	

Foreword

This inaugural MISI newsletter on the applications of imaging in infectious diseases comes at a critical time when we are rising to meet the COVID-19 pandemic, one of the greatest challenges of our times. The scientific community, including biomedical imaging scientists, are showing remarkable resilience in the face of this challenge. Molecular and functional imaging technologies have many important roles to play in meeting the challenges presented by infectious diseases, ranging from early detection, to monitoring response to treatment, to designing nanoparticle/image-guided therapeutic interventions for treatment. Several of these aspects are covered in the newsletter with contributions from leading researchers in the field. While the pandemic has negatively impacted almost every aspect of our existence, it has highlighted the importance of global co-operation in meeting such a challenge. This newsletter plays an important role in the exchange of ideas and advances in the applications of molecular and functional imaging to address important problems in infectious diseases.

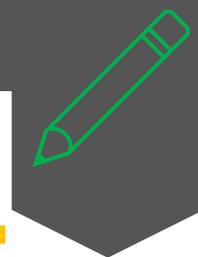


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FROM THE EDITORIAL DESK...



MISI would like to invite all its members to the inaugural quarterly newsletter. We are happy to be back in the fray although we know these are not the best of times. We wish to make a small beginning with this effort. The global pandemic has brought to fore like nothing else in recent times the importance of diagnosis. Scientists world over are racing against time to develop new drugs and vaccines. As a community we have a significant role to play in this endeavour. This is what made us decide that our first newsletter's focus being on infectious diseases would be apt. We have invited leaders from various fields to contribute who graciously accepted our request. We wanted to give a comprehensive view of current trends. We have showcased members and their work. We wish to choose other themes in the future for which we welcome your contributions and suggestions. Our focus will be on encouraging young researchers especially women scientists. We plan to conduct national and international webinars in the future based in various other topics for which we would like your suggestions with regard to choosing topics which will benefit our community most. We plan to work closely with WMIS (World Molecular Imaging Society) and FASMI (Federation of Asian Societies of Molecular Imaging) at various levels. We look forward to your active participation and request you to spread the word about our activities. Stay safe and healthy.



DR. JYOTSNA RAO &

PROF. UMA MAHESWARI KRISHNAN





About us...

The Molecular Imaging Society of India (MISI) was started in 2014 as the Indian affiliate of the World Molecular Imaging Society (WMIS) at the instance of Dr. Zaver Bhujwala, Professor & Director, Division of Cancer Imaging Research, Johns Hopkins School of Medicine and the then president of WMIS. It was incubated by Piramal group with Dr. Swati Piramal serving as the first President of the Society. MISI was formally inaugurated as the Indian affiliate of WMIS on 9th March, 2014 at Piramal Research Centre, Mumbai.

MISI is a non-profit society registered under the Societies Registration Act, 1860 and Societies Registration (Maharashtra) Rules, 1971. The mandate of MISI focuses on all modalities of molecular imaging that includes functional MRI, Gamma camera, SPECT, PET, MR Spectroscopy, optical imaging, molecular ultrasound imaging, radioimaging and other emerging imaging tools. Currently, Dr. Jyotsna Rao, Consultant, Nuclear Medicine and PET-CT at Apollo Gleneagles PET-CT Center, Hyderabad, has currently taken over as the President of MISI and Prof. Uma Maheswari Krishnan, Dean of School of Arts, Sciences & Humanities, SASTRA Deemed University is the Secretary of MISI. Dr. Deepak Behera, Managing Director, Medical Imaging Consultancy, USA has been appointed as the Director, Executive strategy & Alliances. Four seminars have been organized by MISI over the years that covered all major molecular imaging modalities and their applications towards personalizing patient care. This quarterly newsletter is an effort to extend the reach of MISI to its members and associates, and serve as an interaction platform between practicing clinicians, basic researchers, engineers and industry to discuss, deliberate on the trends, concerns the community faces and use this as a platform to put-up the community's concerns to the regulator. MISI would also like to nurture knowledge networking to enhance the chances of discoveries to be taken up for routine clinical practice. We look forward to your participation in MISI and its activities as a member. The registration details are provided in the membership form given in the following section.

Personal Information

Name in full (BLOCK LETTERS) _____

Gender and DOB (DDMMYY) _____

Nationality _____

Permanent Address _____

Personal contact number _____

Personal Email _____

Professional Information

Professional Qualification _____

Designation and organization _____

Special experience in the area of
Molecular Imaging
(Additional sheet may be used) _____

Official Address _____

Work Phone _____

Email _____

Membership Information

Membership requested* Life/Corporate/Student/Annual

Cheque No./DD No. & Date _____

Amount (Rs.)* _____

Signature _____

*Please fill this membership form & attach a Cheque/DD favoring "Molecular Imaging Society of India" payable at Mumbai, towards membership fee and send it to Dr. K. Uma Maheswari, Secretary, Molecular Imaging Society of India, SASTRA Deemed University, Thanjavur, Tamil Nadu 613 401. Alternately, online transfer could be made to: HDFC Bank, Fort Branch, Mumbai (Molecular Imaging Society of India, Account number: 501000 92524491; IFSC: HDFC0000060). The receipt and membership certificate will be sent to you by email.

Category	Indian (Rs.)	Foreigner (USD)
Student	500	25
Annual	1000	75
Life	5000	200
Corporate	10000	500

IMAGING INFECTIOUS DISEASES - A CLINICIAN'S PERSPECTIVE

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Introduction

As with any other branch of medicine, the objective of patient evaluation in the field of Infectious Diseases (ID) is the correct diagnosis of the patient's condition/illness. The right diagnosis leads to the proper treatment, improvement in the patient's symptoms and well-being,

and reduction of human suffering. One famous ID professor keeps saying, "The diagnosis is not everything. It is the only thing!" Considering the above, making the correct

diagnosis is of paramount importance in ID (or in any branch of medicine, for that matter). Radiology is central to this process and plays a crucial role. A discussion on the role of imaging in every infectious disease would itself constitute a voluminous book. Hence, this article will be restricted to the more common uses of imaging in ID.

Some aspects have been highlighted more than others.

Respiratory infections

Let us consider the diagnosis of community-acquired pneumonia: The presence of an infiltrate on a plain chest radiograph is regarded as the gold standard for diagnosing pneumonia when clinical and

microbiologic features are supportive. In the case of upper respiratory infections: imaging is not indicated in patients with clinically diagnosed

"THE DIAGNOSIS IS NOT EVERYTHING. IT IS THE ONLY THING!" - MAKING THE CORRECT DIAGNOSIS IS OF PARAMOUNT IMPORTANCE IN ID (OR IN ANY BRANCH OF MEDICINE, FOR THAT MATTER).

uncomplicated rhinosinusitis. If obtained, findings consistent with acute rhinosinusitis on CT include air-fluid levels, mucosal oedema, and air bubbles within the sinuses. However, these findings are nonspecific. Mucosal abnormalities are common among asymptomatic adults, and mucosal oedema, air bubbles, and air-fluid levels have also been observed in



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patients with the common cold. Plain films are also unhelpful due to poor sensitivity and specificity.

In stark contrast, imaging is paramount for the management of fungal rhinosinusitis. It would suffice to say that CT and MRI play a crucial role in the diagnosis of fungal balls, allergic fungal sinusitis, and invasive fungal sinusitis.

Skin and soft-tissue infections (SSTIs)

Overall, the role of imaging is limited in SSTIs because the diagnosis

and management are mainly clinical. In the case of soft tissue infections, the best initial radiographic imaging exam is a CT scan. The most useful finding is the presence of gas in soft tissues, which is seen most frequently in the setting of clostridial infection or polymicrobial (type I) necrotizing fasciitis. This finding is highly specific for necrotizing soft tissue infections (NSTI) and should prompt immediate surgical intervention. Other radiographic findings may include fluid collections, absence or heterogeneity of tissue enhancement with intravenous contrast, and inflammatory changes beneath the fascia.

MRI has a limited role in NSTI because it is not as useful as CT for the detection of gas in soft tissues and is overly sensitive. Ultrasound will only demonstrate soft tissue swelling but cannot determine aetiology (infection/inflammation/tumour).

Bone and joint infection

Imaging is invaluable in bone and joint infections. Plain radiography will suffice in most cases of septic arthritis. It will not provide a definite diagnosis but can be used in the follow-up of patients. CT/MRI is valuable in case of hip/sacroiliac septic arthritis.

In cases of non-vertebral osteomyelitis, imaging should begin with conventional radiographs of the involved area. A more sophisticated imaging modality should be pursued for patients with normal radiographs or radiographs suggestive of osteomyelitis without definitive

characteristic features; such imaging may be used to establish a diagnosis of osteomyelitis and/or to define the extent of disease for surgical planning. In general, MRI is the imaging modality with the greatest sensitivity for the diagnosis of osteomyelitis; if MRI is contraindicated, a labelled leukocyte scan, CT, or PET/CT is appropriate.

MRI is the most sensitive radiographic technique for diagnosis of vertebral osteomyelitis and epidural abscess. CT is a reasonable alternative imaging modality when MRI is not available. If neither CT nor MRI is available, plain films should be pursued; however, plain films typically demonstrate radiographic findings only after the disease has become advanced. If a plain film demonstrates vertebral osteomyelitis, additional imaging is still warranted to assess the extent of disease and the presence of complications (epidural or paraspinal abscess). Radionuclide scanning may be useful if MRI is contraindicated because of claustrophobia or presence of an implantable cardiac or cochlear device.

Urinary tract infections

Radiographic evaluation is warranted in all neonates with UTI. The first step of this evaluation is renal ultrasonography to identify structural abnormalities. Also, voiding cystourethrogram (VCUG) is recommended to evaluate for vesicoureteral reflux (VUR) in neonates with abnormal renal ultrasound, non-E. coli pathogen, or recurrent UTI. USG, VCUG and renal

scintigraphy play an important role in the diagnosis and management of urinary tract infections in infants older than one month and young children.

Most adult patients with complicated acute UTI in adults do not warrant imaging studies for diagnosis or management. Imaging is generally reserved for those who are severely ill, have persistent clinical symptoms despite 48 to 72 hours of appropriate antimicrobial therapy, or have suspected urinary tract obstruction (e.g., if the renal function has declined below baseline or if there is a precipitous decline in the urinary output). Imaging is also appropriate in patients who have recurrent symptoms within a few weeks of treatment. The main objective of imaging is to evaluate for a process that may delay response to therapy or warrant intervention, such as calculus or obstruction, or to diagnose a complication of infection, such as a renal or perinephric abscess. Imaging should be obtained urgently in patients with sepsis or septic shock to identify any evidence of obstruction or abscess that requires urgent source control.

CT scanning of the abdomen and pelvis (with and without contrast) is generally the study of choice to detect anatomic or physiologic factors associated with complicated acute UTI. CT, without contrast, has become the standard radiographic study for demonstrating calculi, gas-forming infections, bleeding, obstruction, and abscesses. Contrast is needed to

demonstrate alterations in renal perfusion. CT findings of pyelonephritis include localized hypodense lesions due to ischemia induced by marked neutrophilic infiltration and oedema. When there is suspicion for prostatitis, a trans-rectal USG or MRI pelvis is preferred.

CNS infections

A head CT should be performed (to exclude a mass lesion or raised ICT) before LP in adults with suspected bacterial meningitis who have one or more of the following risk factors

1. Immunocompromised state (e.g., HIV infection, immunosuppressive therapy, solid organ or hematopoietic cell transplantation)
2. History of CNS disease (mass lesion, stroke, or focal infection)
3. New-onset seizure (within one week of presentation)
4. Papilledema
5. Abnormal level of consciousness
6. Focal neurologic deficit

In patients presenting with suspected encephalitis (altered mental status plus fever/seizures), CT scanning is useful to rule out space-occupying lesions. MRI is sensitive for detecting demyelination, which may be seen in other clinical states presenting with mental status changes (e.g., acute disseminated encephalomyelitis [ADEM] or possibly a relatively rapid presentation of progressive multifocal leukoencephalopathy). If present, the

location of an abnormal signal can sometimes be suggestive of specific etiologies:

1. Temporal lobe involvement is strongly suggestive of herpes simplex virus (HSV) encephalitis, although other herpes viruses (e.g., VZV, Epstein-Barr virus, human herpes virus 6) can also produce this clinical picture
2. Involvement of the thalamus or basal ganglia may be observed in the setting of encephalitis due to respiratory viral infection, Creutzfeldt-Jacob disease, arbovirus, and tuberculosis. Dengue and chikungunya encephalitis, seen widely across India, may be considered in the appropriate clinical and radiology features.
3. In patients with West Nile infection, MRI imaging demonstrates a variety of abnormalities in the basal ganglia, thalami, mesial temporal structures, brainstem, and cerebellum with/without abnormalities noted in the spinal cord and cauda equina.
4. The presence of hydrocephalus may suggest nonviral etiologies such as bacteria, fungal, or parasitic agents
5. MRI during post-infectious encephalitis may demonstrate multifocal lesions mainly involving supratentorial white matter

MRI is more sensitive than CT for the diagnosis of brain abscess.

COVID-19

Chest X-ray may be normal in early/mild. At least 20% of symptomatic patients will have a normal CXR throughout their illness. Although chest CT may be more sensitive than chest radiograph and some chest CT findings may be characteristic of COVID-19, no finding can completely rule in or rule out the possibility of COVID-19. In the United States, the American College of Radiology (ACR) recommends not using chest CT for screening or diagnosis of COVID-19 and recommends reserving it for hospitalized patients when needed for management.

When reporting chest CTs in patients with symptoms of COVID-19, two systems may be used:

1. The Radiological Society of North America (RSNA) has categorized features as typical, indeterminate, or atypical for COVID-19, and has suggested the corresponding language for the interpretation report.
2. CO-RADS, for COVID-19 Reporting and Data System, is a categorical assessment scheme for chest CT in patients suspected of COVID-19, representing the level of suspicion for pulmonary involvement. The substantial agreement among observers and its discriminatory value make it well-suited for use in clinical practice. CO-RADS 1-6 represents an increasing level of suspicion for COVID-19 with one indicating no

suspicion, and six indicating PCR positive (2,3, 4 and 5 represent low, intermediate, high and very high-suspicion).

Chest CT abnormalities are more likely to be bilateral, have a peripheral distribution, and involve the lower lobes. Less common findings include pleural thickening, pleural effusion, and lymphadenopathy.

Chest CT abnormalities have also been identified in patients before the development of symptoms and even before the detection of viral RNA from upper respiratory specimens. However, the chest CT may be normal (in up to 50% in one study) inpatients with early disease (CT performed \leq 2 days after symptom onset).

CT chest can be considered to play the following role in COVID-19:

1. In patients with suggestive symptoms but negative PCR, a 'positive' CT indicates possible COVID-19 disease and need for repeat/better (lower respiratory

tract sampling such as endotracheal aspirate or bronchoalveolar lavage) PCR testing.

2. There is some evidence to suggest that CT may delineate patients into two different respiratory phenotypes that need to be managed differently.

3. CT will aid in the diagnosis of pulmonary thromboembolism [CTPA].

The major caveat in the utility of imaging is ID is that, in some cases, radiology cannot provide a definite diagnosis. Patients with enteric fever, scrub typhus, leptospirosis, melioidosis and complicated malaria can all have pulmonary opacities. In some cases, radiology is invaluable: diagnosing a renal cell carcinoma in a patient with PUO, the diagnosis of progressive multifocal leukoencephalopathy (PML) in a patient with advanced HIV-AIDS and the diagnosis of emphysematous

pyelonephritis in an uncontrolled diabetic with septic shock.

However, in almost all cases in ID, radiology cannot provide an etiological diagnosis. A patient with fever, cough, weight loss, history of contact with TB with a right upper zone cavitory lesion may very well be considered to be having tuberculosis until proven otherwise. However, the sputum/BAL may reveal no cardiosis, non-tuberculous mycobacteria or, once in a lifetime, *Rhodococcus equi*. A patient with acute myeloid leukaemia and a febrile neutropenic fever with a 'halo-sign' on CT may have invasive pulmonary aspergillosis but may also have mucormycosis, fusariosis (caused by *Fusarium* species) and scedosporiosis (due to *Scedosporium apiospermum* complex).

Until January 2020, a patient with fever, cough, dyspnea and bilateral, peripheral, subpleural ground-glass opacities would not have been considered to have COVID-19 too!



Interesting snippets - Milestones in medical imaging #1

Discovery	Year
Magnifying glass	1250
Light microscope used by Antonie von Leeuwenhoek	1660
Eye glasses	1752
X-ray produced by Wilhelm Roentgen	1895
Chest X-ray used to detect tuberculosis	1900
First contrast filled image of kidneys	1906

MOLECULAR IMAGING IN INFECTIOUS DISEASES: A PRECLINICAL PERSPECTIVE

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Introduction

Infectious diseases are one of the leading causes of death in the world. Majority of these deaths are due to a few pathogens which include bacteria, viruses, fungi and parasites. The significant increase in antimicrobial resistance (AMR) has become a considerable burden on healthcare costs, especially as commodity

comorbidity in immune-compromised patients. It is anticipated that the number of deaths due to AMR would reach more than 10 million per

year by 2050. The impact of AMR could potentially be reduced by improved diagnosis and an enhanced understanding of the molecular mechanisms involved in infectious disease pathology. While several technologies have been introduced in recent times to address this issue, one that has gained prominence is molecular imaging.

Molecular imaging constitutes non-invasive technologies which have

great utility in understanding the molecular mechanisms of a disease state. Several of the molecular imaging techniques including PET, MRI, CT, US, BLI and Immuno PET/CT have been used successfully in the preclinical settings to improve our understanding of the infectious disease process. This article will provide a birds' eye view of the

THE USE OF MOLECULAR IMAGING TECHNIQUES WHICH ARE SIMILAR BETWEEN ANIMALS AND HUMANS ALLOWS FOR A SEAMLESS TRANSFER OF TECHNOLOGY AND CORRELATION BETWEEN THE PRECLINICAL AND CLINICAL SETTINGS.

molecular imaging techniques that have been used in elucidating some of the critical characteristics of infectious diseases, which have a significant contribution to the healthcare costs in India. The article will also cover the use of molecular imaging techniques used in the drug discovery and development process.

Molecular imaging in Drug Discovery & Development



Dr. Shridhar has more than 16 years of drug discovery and development experience in Indian pharmaceutical industry in various therapeutic areas. Shridhar is a Ph.D. in Pharmacology from Ohio State University, and has post-doctoral experience in Neuropharmacology at the University of California, Los Angeles. Shridhar, a serial entrepreneur, is currently Founder Director and Chief Executive Officer of Foundation for Neglected Disease Research (FNDR), a not-for-profit company with a mission to discover and develop drugs for diseases of the developing world. Throughout his career, Shridhar has overseen the Discovery and Development of 18 clinical candidates in the areas of infection, oncology, diabetes, inflammation, and respiratory diseases. As part of FNDR, Shridhar has managed to raise donations worth 2.0 million USD from AstraZeneca, more than 1.7 million USD in grant money from the funding agencies and around 5 million USD in investment into preclinical and clinical asset development by partners over the last 4 years. He may be reached at shridhar.narayanan@fnldr.in

Vidya is a microbiologist with vast experience in Actinomycete and Eubacteria Isolation, Culture Library for Actinomycetes and Eubacteria, Metabolite Library, Anti-infective Screening, Fermentation Studies, Database for culture Maintenance, Fermentation and Preservation.

Drug discovery and development (DD&D) is a long process, and it takes about 8 to 12 years and more than 1.4 billion USD for a single drug to reach the market. This is due to the more than 95% failure rate when going through the various steps in this process. Any improvement in the different steps involved in DD&D can result in significant time and financial savings.

The process of DD&D starts with selecting a disease and a specific biological target responsible for the pathophysiological aspects of that disease. This biological target is then modulated using either a small molecule or large molecule (antibody) resulting in resolution of the pathology. Multiple iterations are then carried out in the lead identification to identify a lead candidate. The lead candidate is then optimized for various properties like solubility, tissue distribution, etc., using *in vitro* and *in vivo* systems to identify a preclinical candidate. The preclinical candidate is evaluated in an appropriate animal model for safety, and toxicological evaluation, which is required for regulatory submissions, are conducted. If there are no significant adverse events, the molecule is nominated as a clinical candidate to be tested in humans.

Molecular imaging is a tool that can enable some of the steps of DD&D process and make it more efficient. Molecular imaging techniques such as PET or SPECT can be used in the early phase of drug discovery to identify

drug targets, understanding their distribution in tissues and interactions between a potential drug and a drug target. Reporter gene imaging techniques have also been used as tools for understanding this process.

Imaging techniques can be used to understand the drug absorption, distribution, metabolism and excretion, which can define the utility of a molecular scaffold for a disease. The ability to do longitudinal real-time measurements in an animal model using imaging enables the efficient use of animals and helps reduce their numbers used in experimentation. The findings from such Imaging studies can be readily extrapolated to a clinical situation involving a patient.

Viral diseases

The emergence of the novel coronavirus SARS-CoV-2 as a pandemic has created an urgent need for suitable animal models and analysis techniques to aid the diagnosis and the treatment of this disease. Recently MI Labs one of the pioneers in CT systems enhanced its preclinical U-CT system to allow for non-invasive ultra-high-resolution imaging of the lungs. This enabled researchers to locate the pathological processes occurring as a result of the infection to the bronchi of the different animal models used, including mice, guinea pigs and ferrets.

FDG PET/CT, which is a sensitive method to detect and monitor diseases such as viral pandemic can be effectively used to diagnose and monitor disease progression. A

correlation between higher FDG uptake and time to heal in lung lesions of COVID-19 patients has been suggested by Qin et al. (European Journal nuclear medicine and molecular imaging 2020).

Bioluminescence imaging has been widely used to track organisms causing infectious diseases. In a murine herpes virus model, Kang et al. have monitored CNS infection by the virus using BLI. They have demonstrated that the brain is a site for latent viruses. This finding has implications in the understanding of the role of viruses in neurological diseases.

Bacterial diseases

Tuberculosis caused by *Mycobacterium tuberculosis* is the leading cause of death among infectious diseases. India alone contributes to more than 25% of the global TB burden, with more than 2.8 lakhs deaths every year. Significant challenges with this ancient disease remain the timely diagnosis of the disease and requirement of long-term treatment with a combination of drugs, six months for drug-sensitive and 18 to 24 months for the drug-resistant variety of TB. The traditional method of confirming TB with acid-fast staining and microscopy is time-consuming and fraught with errors due to a multitude of reasons.

Blanc et al. have used MALDI-MSI (MALDI Mass Spectroscopy Imaging), a technique which is capable of visualizing analytes in tissue sections using label-free technology. Sarathy et

al. have also used imaging techniques to study the drug distribution and found that the distribution of drugs in the necrotic lesions can be heterogeneous and sub-optimal. Their ability to visualize drug distribution along with the bacterial biomarkers will allow for analyzing drug activity in an entire system. This would be of immense value, particularly in diseases like TB, which are plagued by problems with drug distribution at the target site.

Studies by Davis et al. using SPECT imaging in mice infected with an engineered strain of Mycobacterium tuberculosis expressing thymidine kinase have shown the power of this technique to identify very few TB organisms within a granuloma. This method can be used to test the efficacy of newer drug regimens which can be used and monitored in humans.

Fungal diseases

Aspergillus fumigatus causes a fatal lung disease called invasive pulmonary aspergillosis in immune-compromised patients. Rolle et al. have used a novel antibody guided positron emission tomography and magnetic resonance imaging to detect the fungi in the lungs. This technique allowed the researchers to distinguish the bacterial and fungal lung infections, and if used in the clinic could potentially guide the treatment regimen being administered to the patients. Pfister et al. have used hybrid imaging technology using a Ga labelled siderophore to identify infected versus

un-infected areas in the lungs of these patients.

Slesiona et al. used bioluminescence to demonstrate the persistence of Aspergillus terreus conidia. Such BLI technique can be used not only for the detection but also to monitor the treatment success in long term infections.

Parasitic diseases

Malaria caused by the infection with Plasmodium falciparum or Plasmodium vivax accounts for nearly half a million deaths every year. Most of these deaths are due to cerebral malaria and severe complications of this disease. Cerebral malaria results in several pathophysiological changes including a reduction in cerebral blood flow, sticking of the RBC to the walls of blood vessels and metabolic disturbances in the host brain.

A mouse model developed using the ANKA (Antwerpen-Kasapa) strain of Plasmodium berghei results in cerebral malaria, which allows for imaging of the brain. The characteristic features of this model, including the breakdown of the blood-brain barrier, haemorrhage, reduced blood flow to the brain, oedema of the brain was elucidated by Saggiu et al. using advanced MRI techniques. They also detected early changes which included damage to the trigeminal and optic nerves. These features are now being explored for the early detection of cerebral malaria in humans.

Intravital microscopy is a technique that allows for the long-term imaging of a particular region of

the brain to compare the microvascular changes resulting in the pathophysiology of cerebral malaria. Cabrales and coworkers used this technique to demonstrate the importance of calcium channels in the changes to cerebral microvasculature in CM. They treated ANKA infected mice with nimodipine and showed a reversal in the changes to microvasculature using the intravital microscopy. Others have also used this technique to demonstrate the utility of exogenous nitric oxide (Cabrales) in reducing the vascular leakage associated with CM.

Conclusion

The use of molecular imaging techniques which are similar between animals and humans allows for a seamless transfer of technology and correlation between the preclinical and clinical settings. This can provide for faster and appropriate treatment modalities being used in patients resulting in better outcomes.

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Interesting snippets - Milestones in medical imaging #2

Discovery	Year
Barium sulphate used as contrast agent for gastro-intestinal tract	1910
Radiographic imaging of gall bladder, bile duct & blood vessels	1924
Transmission electron microscope constructed	1932
Coronary artery imaging	1945
Panoramic x-ray imaging of jaw and teeth; dynamic x-ray imaging	1955
Fiber endoscopy	1957
Fetal Ultrasound	1960
Commercial Ultrasound	1965
X-ray mammography	1970
CT scanning	1972
Coronary angioplasty	1976

IMAGING STOCHASTIC GENE EXPRESSION OF HIV-1

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Introduction

Here we describe how HIV-1 exploits gene expression noise to switch between transcriptionally active and silent states. Understanding how this molecular viral switch works is critical towards finding a solution to the 'functional cure' of HIV-1.

In biology, variability is inevitable, and every living individual in a population is unique. Much of this variability in a population arises due to

THE APPLICATION OF MOLECULAR IMAGING TECHNIQUES AT THE SINGLE-CELL LEVEL HAS BECOME INSTRUMENTAL IN EVALUATING STOCHASTIC GENE EXPRESSION.

differences encoded at the genetic level. However, phenotypic variability is observed even in a cell population with identical genetic content under a homogenous environment. This non-genetic variability among an isogenic population is a result of random fluctuations in gene expression or gene expression 'noise' (Raj A et al., Cell 2008, PMID: 18957198).

Noise in a cell population arises due to fluctuation in biochemical processes such as transcription, translation,

splicing, etc. Gene expression noise confers fitness advantage for survival and has been shown to critically influence probabilistic fate decisions in viruses, prokaryotes, and eukaryotes. For instance, increasing noise in stress-related yeast proteins

provides a selective advantage to a fraction of yeast cells to keep the levels of stress-related proteins above a critical threshold (Blake WJ et al., Mol Cell 2006, PMID: 17189188).

Likewise, noise in λ -phage regulatory circuit, under fluctuating host environment, influences switch between two developmental fates: lytic cycle and lysogeny (Arkin A et al., Genetics 1998, PMID: 9691025).

Following the integration of HIV-1 into the host genome, the provirus must choose between two mutually exclusive infection fates: active replication, leading to successful virus production, or proviral latency,

Ranga obtained a Ph.D. from The Jawaharlal Nehru University, School of Life Sciences, Delhi, India in 1990 for the immunochemical characterization of the soluble antigens of Mycobacterium tuberculosis under the supervision of Prof. Rajiv K Saxena. During his first post-doctoral training with Dr. Indira K Hewlett, CBER, Food and Drug Administration, USA (1991-1993), he developed and optimized multiplex amplification detection of HIV-1 and HIV-2 co-infections. During the second post-doctoral tenure with Dr. Gary J Nabel, University of Michigan (1993-1997), Ranga played a pivotal role in evaluating the efficacy of a gene therapy strategy to protect HIV-infected T-cells in the first FDA approved clinical study. Additionally, he developed an HIV-1 chimera promoter under the control of the CD4 enhancer with an aim to restrict gene expression of therapeutic genes to the CD4 cell. He established an HIV laboratory at JNCASR, Bangalore in 1997. Ranga has been working with HIV for the past 25 years. He is a member of the Trainee Selection Panel, AIDS International Training and Research Program of the Albert Einstein School of Medicine, New York. He is also a member of various other National and International societies such as the American Society of Microbiologists, International AIDS Society, National Immunology Society and Molecular Immunology forum. He can be reached at udaykumar@incasr.ac.in

leaving the virus in a transcriptionally silent state - an ultimate obstacle towards a 'functional cure'. The switch between these two infection fates of the virus is controlled by Tat, the

master regulator of transcription that establishes a positive-feedback loop, and a multitude of host and epigenetic factors. HIV-1 promoter is inherently noisy as compared to any other cellular promoters. The inherent noise of the viral promoter is subsequently amplified many folds by the downstream Tat positive-feedback loop; thus, greatly influencing the active versus latent decision making. The bursty nature of viral transcription is due to competitive binding of activators, repressors, and chromatin remodelers to the multiple transcription factor binding sites occurring in tandem and close proximity in the viral promoter. Additionally, HIV-1 exhibits a high degree of genetic variability due to its high replication rate. Any mutation at the key regulatory element leads to modulation of transcriptional dynamics (transcription burst size and frequency), thereby influencing latency decisions.

How do we study noise in HIV-1 gene expression? Until recently, scientists studied gene expression only at the level of the population - a strategy limited by averaging the heterogeneity among individual cells. It was not possible to examine the

transcriptional dynamics of each cell at the population level. With the advent of single-cell molecular imaging techniques, determining the number of mRNA/proteins in a cell and variation among the population has become straightforward. The variability in a population, an estimate of gene expression noise, is calculated in terms of coefficient of variance (CV), the ratio of the standard deviation to mean of the population (see Figure-1 next page).

To determine noise in HIV-1 gene expression, we employ a sub-genomic HIV-1 lentiviral vector that co-expresses a destabilized green fluorescent protein (d2EGFP) and Tat under the control of HIV-1 LTR, the promoter of the virus. The activity of the promoter is determined by monitoring the expression levels of the short-living d2EGFP (a half-life of approximately 2 h). Jurkat T-cells are infected with the reporter lentiviral vector at ~0.1 MOI to ensure a single integration event of the virus per cell. The infected cells are sorted by flow cytometry to generate a clonal cell population. Different clonal cell populations are activated with a cocktail of mitogens after immobilizing them on a glass-bottom micro-slide

and followed using an automated time-lapse live-cell confocal microscope for 15-18 h. Images are captured in multiple planes at an interval of 10 minutes for multiple fields. As shown in the figure, the single-cell trajectories are extracted from the acquired images after background subtraction, and the coefficient of variation is calculated.

However, one of the limitations of this study is the use of d2EGFP, which has a half-life that does not mimic transcript half-life. Further, d2EGFP is typically measured in arbitrary fluorescence units rather than molecular units that prevent the quantitative estimation of molecules. A more direct approach for studying stochastic gene expression would be the quantification of transcripts across different cells in a population. This can be performed using single-molecule fluorescence in-situ hybridization (sm-FISH). Furthermore, transcriptional dynamics can be evaluated using MS2-tagging technique, where mRNA dynamics can be followed in the context of a live-cell. The application of molecular imaging techniques at the single-cell level has become instrumental in evaluating stochastic gene expression.



**Turn to page number 46 to read
Focus Interview by Dr. MKC**

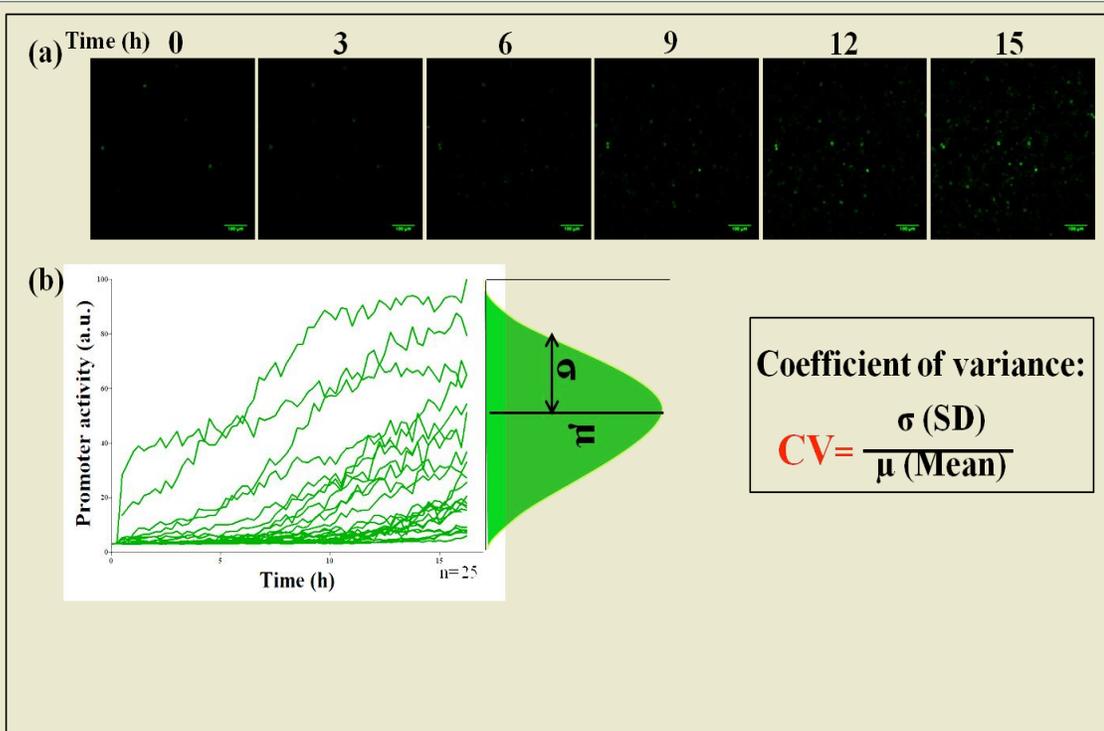


Figure-1: (a) Time-lapse live-cell confocal microscopy snapshots of HIV-1 infected Jurkat T-cells at different time points. (b) Time-lapse d2EGFP trajectories of individual HIV-1 infected cells. A plot of raw d2EGFP trajectories (promoter activity) versus time obtained after background subtraction of a time-lapse confocal microscopy movie of HIV-1 infected cells imaged for 18 hours. Each trajectory represents an individual cell. Variability in the population was determined by calculating the coefficient of variance (CV).

**Multi-photon Laser Scanning
Microscope – Page number 48**

**Opinion – Dr. Deepak - Page
number 53**

PERSPECTIVE: COVID-19- A WAKE-UP CALL FOR INFECTIOUS DISEASES IMAGING

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Since the discovery of $[^{18}\text{F}]$ Fluorodeoxyglucose (FDG) in 1976, radiopharmaceuticals and positron emission tomography (PET/CT) imaging has played an important role in the clinical management of oncology patients. The power of PET includes the ability to follow physiological processes like glucose metabolism in the whole body with exquisite sensitivity (10^{-12}M) and high spatial resolution ($\sim 5\text{mm}$ half width at half maximum) [1]. Moreover, in contrast to single photon emission computed tomography (SPECT)

imaging, PET imaging offers dynamic, quantitative data sets with which tracer kinetic modeling can be done. The widespread use

IMAGING CAN PLAY A POWERFUL ROLE IN THE CLINICAL MANAGEMENT OF PATIENTS SUFFERING FROM BACTERIAL OR VIRAL INFECTIONS.

of $[^{18}\text{F}]$ FDG in oncology, paved the way for molecular imaging research and led to the development and clinical translation of various PET tracers including $[^{68}\text{Ga}]$ DOTATATE and $[^{68}\text{Ga}]$ PSMA. In an elegant perspective written for Science Translation Medicine in 2019, Ordonez et al

summarized the years of research and investment that has gone into developing PET tracers for oncology in contrast to the investment in infectious diseases [2]. As was pointed out in this article, the Molecular Imaging and Contrast agent database (MICAD) lists as many as 5359 PET tracers that have been developed for Oncology as opposed to just 13 PET tracers for Infectious Diseases. However as we have seen with the COVID 19 pandemic, the burden from infectious diseases

has enormous ramifications and we need to increase our investment into better diagnosing and managing infectious disease patients.

Despite the insufficient attention it has received, there have been several novel PET tracers that have been developed to image bacterial infections in the last 5 years including, $[^{18}\text{F}]$ Fluorodeoxy-sorbitol, $[^{11}\text{C}]$ PABA,



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$[^{11}\text{C}]$ -D Alanine, $[^{18}\text{F}]$ Fluoromaltotriose and many others in the pipeline [3]. While all of these newer tracers target different features of bacterial metabolism, other strategies to image bacterial infection include the use of radiolabeled

antibiotics like [¹⁸F]Fluoropropyl trimethoprim, [¹¹C]Rifampicin, [⁷⁶Br]Bedaquiline or to image the immune microenvironment using well-established tracers like [¹⁸F]FDG or [¹⁸F] DPA-714 [3]. All of these tracers in the pipeline are targeting bacterial pathogens. There have been far fewer efforts to develop agents targeting fungal, viral and parasitic pathogens. COVID 19 will change this and we are now seeing a renewed interest in developing new ways to image viral infections. The same strategies applied to imaging bacterial infection can be applied to other pathogens i.e., a) develop pathogen specific tracers, b) target immune environment and c) radiolabel therapeutics targeting specific pathogens. Imaging the immune microenvironment can be particularly important for viruses. T cell driven immune responses drive viral pathogenesis. Hence, tracers that target T cell markers can be used to track viral load and monitor anti-viral treatment. There are a whole host of tracers that are being developed by multiple investigators to image T cells including small molecule based like [¹⁸F] Ara G, [¹⁸F] CFA and antibody/protein based like [⁸⁹ Zr]

malDFO-169, [⁶⁴Cu] Ox40 and many others [4].

There are additional considerations that must be taken into account while investing in the development of PET tracers for infectious diseases. Unlike oncology, in infectious diseases the PET tracers might not play a role in the initial diagnosis of a bacterial infection. This is usually done in an outpatient setting and is heavily dependent on emerging point of care diagnostics. In addition, determining the exact identity of the pathogen is crucial in the management of patients with infections. This can usually be done by PCR or sequencing based approaches. The infectious disease specific PET tracers will play a role in the hospital setting where it is crucial to confirm that a patient with a suspected bacterial infection truly has a bacterial infection, to localize the site of infection, to determine the extent of the infection and to monitor the response to treatment (Figure 1). The last point is truly the most important as in many clinical indications like tuberculosis, osteomyelitis or endocarditis, patients are put on prolonged courses of antibiotic treatment with the clinicians unable to determine if the patient is responding to the treatment or not.

In conclusion, COVID 19 has reinforced what infectious disease physicians and the Gates Foundation have been saying for years: 'infectious diseases are here to stay'. As a society we need to be prepared to face the next crisis. Imaging can play a powerful role in the clinical management of patients suffering from bacterial or viral infections. The last decade has seen the pre-clinical development of a multitude of PET tracers that could be used to image both bacterial and viral infection. The forthcoming decade will see the gradual clinical translation of these tracers. This is where countries like India could play a very important role by collaborating and participating in the clinical trials. Due to the higher prevalence of infectious diseases in India, Indian physicians and scientists have gained a wealth of knowledge and have much to offer to the scientific community as a whole.

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Up Next: Radiology of COVID-19: The basics



Blood/Tissue culture

Emerging point of care diagnostics



Whole Body Imaging (PET/CT, MRI, PET/MRI)

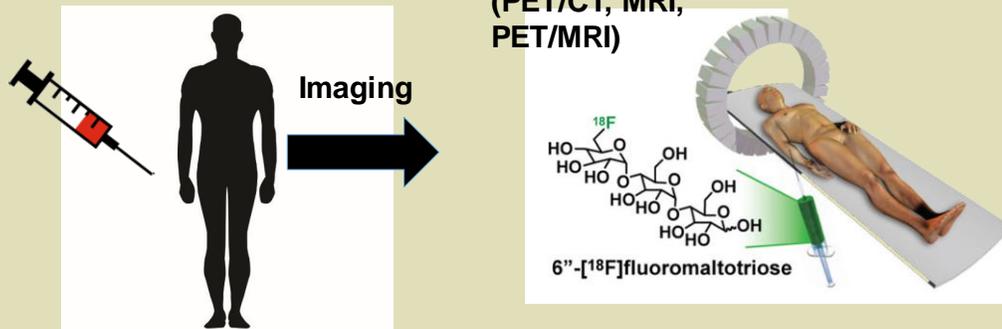


Figure-1: Schematic representation of the role of PET/CT imaging in the diagnosis and monitoring of patients with infectious diseases.

RADIOLOGY OF COVID-19: THE BASICS

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The ongoing SARS-CoV2 (COVID-19) viral pandemic has led to an awareness of just how vulnerable the world's population is to contagious diseases. At the time of this writing, over 8 million people have been stricken with the SARS-CoV2 virus which is the cause of the COVID-19 infection. While most people who have the virus are asymptomatic or exhibit only mild symptoms, those who have

pre-existing conditions (diabetes, hypertension, obesity, elderly) are at most risk for developing the most severe effects of the

disease (e.g. acute respiratory distress syndrome, renal and cardiac failure, neurologic and vascular disease) and death. Although there is still much to learn about the biology of the virus and how to cure and/or prevent the disease through better treatments and vaccine development, there is an ever-increasing number of peer-reviewed publications, reports and descriptions from "boots on the ground" that provide a comprehensive view of the

PATIENTS WITH COVID-19 INFECTIONS HAVE A VARIETY OF SYMPTOMS AND CLINICAL CONDITIONS THAT CAN BE DETECTED AND THEN FOLLOWED BY IMAGING.

viral pandemic. One of the factors for controlling the spread of this highly contagious virus is through adequate testing to find out who is actively infected (through RT-PCR nasal swab testing), who has been exposed and who has recovered (through antibody blood testing) so that appropriate actions can be taken. However, as the detection of the disease has been hampered by

the limited number and distribution of testing kits, many institutions are turning to the use of imaging (chest X-Rays,

CT scans and Ultrasound of the Chest) to look for the tell-tale signs of the disease, particularly in those with moderate to severe symptoms. This article briefly describes the common imaging findings in patients with COVID-19 with special focus on lung imaging

as it is the most common organ of radiographic change. The reader is directed to the online RSNA learning center for a more comprehensive



Dr. Korn completed a Doctor of Philosophy degree in Molecular Biology at Albert Einstein College of Medicine, followed by his Medical training at Stanford School of Medicine. He had his postgraduate training at the Hospital of the University of Pennsylvania. Dr. Korn specializes in Nuclear Medicine and Cancer Biology with extensive involvement in clinical research. Dr. Korn has received public recognition and awards from the American Society of Clinical Oncology, American College of Radiology Imaging Network, Ibis Foundation of Arizona, and received the Top Doctor Award for Radiology and Nuclear Medicine. Though his professional accolades accurately reflect his clinical excellence, his current professional associations, education-based activities, and commitment to clinical research quality make up the core of this professional. He also is an Adjunct Faculty at The Translational Genomics Research Institute, City of Hope, Scottsdale, Arizona. He can be reached at rkorn@imagingendpoints.com

review of the radiology of COVID (<https://www.rsna.org/covid-19>).

In order to understand the imaging findings due to COVID-19, it is

important to recognize how the SARS-CoV2 virus infects different parts of the body. It is believed that the virus enters into healthy cells through the ACE2 receptor. The ACE2 receptor is found in various tissues throughout the body including the nasal passages, lungs, heart, kidney, intestines, brain, blood vessels and certain immune cells required to fight off the disease. The distribution of the ACE2 receptors in our body provide a reasonable explanation for the symptoms seen in people infected with the virus- from nasal congestion and loss of taste and smell, cough, heart attacks, renal failure, strokes, encephalitis, blood clots and end organ failure. A closer look at the concentration of ACE2 receptors in the airways show that the highest concentration is found in the nasal passages with decreasing concentrations noted as you travel distally into the lungs. In the lungs the ACE2 receptors are primarily found on Type II Pneumocytes which are the cells primarily responsible for maintaining patency of the alveoli to allow for adequate exchange of O₂ and CO₂ through the production of surfactant- a molecule that reduces the surface tension of pulmonary fluids and contributes to the elastic properties of the lungs. As a result of the either direct viral infection of these cells and/or damage from the resultant inflammatory response directed by the immune system (cytokine release storm) the Type II Pneumocytes undergo destruction that leads to the common changes that

are seen on Chest CT (Figure 1). These changes include:

- Rounded Ground-glass opacities (GGOs)
- Consolidation
- Intra and interlobular septal thickening (IST)
- Subpleural clearing (SPC)
- Air Bronchograms
- Vascular congestion
- Septal banding
- Diffuse Alveolar Damage

These findings are usually bilateral and begin mainly in the posterior segments of the lower lung lobes following a pattern of involvement that is seen in patients with food or fluid aspiration. This has led to the hypothesis of the virus entering the lung through aspiration of nasal secretions and/or acid reflux (a condition seen more commonly in the elderly and obese). Although the CT chest findings above are typical for COVID-19 they are by no means specific. They can be seen in other viral infections (SARS, MERS, Influenza) and other non-infectious processes that damage the lungs (e.g. inhalation injury, trauma, drug reactions). Therefore, the diagnosis of COVID-19 based upon CT needs to be made in the context of the patient's clinical presentation, risk factors, exposure history with other COVID-19 infected patients and prevalence of the disease in the community. Thus, in the appropriate setting, the sensitivity and specificity of the CT finding can be quite good (70-90% ranges). However, even with such a decent CT diagnostic

performance the use of CT scans as a screening tool is strongly discouraged because of the high false positive and false negative rates in an unselected population. Nevertheless, CT scans can provide critical information to help manage a patient's condition, especially during hospitalization.

The logistics of performing CT chest exams can be challenging, especially in the critically ill patient who has to be moved from the ICU ward, through the hospital corridors and into the CT scanner suite. This operation requires special care as the mere transport and scanning of the patient can lend itself to increased COVID-19 exposure of healthcare staff, technologists and others. Special care is also required to ensure that personal protective equipment is readily available and worn by those directly involved in this process and that special procedures are in place to clean areas of patient contact. In hospitals with limited resources this could place additional burdens on staff to maintain a safe environment. All of these factors have led to reduced access to CT. In lieu of these factors, the use of Chest X-Rays (CXR) has been advocated in patients with suspected or known COVID-19 infections. One of the advantages of CXRs is that it can be done at the patient's bedside and dedicated COVID-19 CXR machines can be assigned. The drawback, however, is that the sensitivity and specificity for detecting COVID-19 infections and complications is much lower than CT (ranges 20-60%). Nevertheless, CXRs

can provide a rapid picture of COVID-19 related infiltrates and helps to rule out complications associated with ventilation support. Another radiologic test at the bedside that is gaining support is the use of Ultrasound (US). US uses non-ionizing radiation in the form of soundwaves as it interrogates the involvement of the lung fields that lie close to the body surface. This point of care exam shows abnormal acoustic shadowing which can be followed up over time as the patient either heals or progresses in their clinical course. It can also be used with special vascular contrast agents to rule out pulmonary embolism.

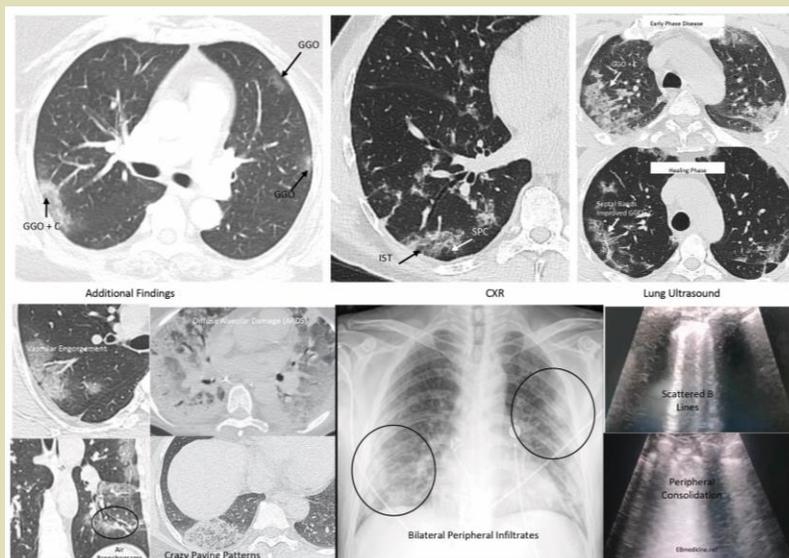
In summary, patients with COVID-19 infections have a variety of symptoms and clinical conditions that can be detected and then followed by imaging. Although CT scans can detect early changes in the course of the disease (prior to nasal swap and blood tests turning positive) its use should

be performed judiciously and to address clinical questions that help better manage a patient. Other techniques, such as CXR and US can be useful as providing point of care service without complicated logistics required to transport the patient for CT scans. Finally, the use of AI and Radiomics- which uses high resolution features on CT scan to better predict the biology, response and need for ventilatory support is being actively pursued in our laboratory as well as others to better predict a patient's outcomes and return to full functional capacity. Although, a modern-day challenge, perhaps some good news regarding COVID-19 is beginning to emerge.

Panel of COVID-19 Images Showing Common Features on CT, CXR and US:

The figure below demonstrates the multiple presentation of COVID-19 Lung Disease during imaging. Early

infection shows bilateral, rounded, peripheral based Ground Glass Opacities (GGO) with or without consolidation (C), Inter and intralobular septal thickening (IST) and subpleural clearing (SPC). These features are compatible with an organizing pneumonia. Upon healing, there can be resorption of GGO ± C with septal band formation. Additional features of COVID-19 CT include vascular engorgement, diffuse alveolar damage, air bronchograms and crazy paving patterns. Pleural effusions, adenopathy and other features are rare. CXR findings can include vague peripheral infiltrates (circles) that are often bilateral and peripheral involving the lower lobes. Bedside Lung US can show so-called scattered B lines due and peripheral consolidation.



ROLE OF ARTIFICIAL INTELLIGENCE IN INFECTIOUS DISEASES

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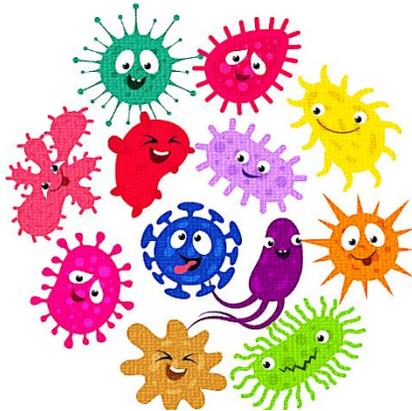
Infectious Diseases and AI

As far as infectious diseases are considered, prevention, monitoring, rapid-response and management efforts to be particularly helpful in decelerating or filibustering outbreaks. Infectious diseases are very challenging to diagnose in the early stage, with excessive failure rate resulting in high fatality and alarming rate of drug resistance.

Artificial Intelligence (AI) and Machine Learning (ML) now becomes a new strategic weapon in the global health care system is now emerging to assist with infectious disease prevention, rapid-response, surveillance and management. One of the most thrives of AI is often seen in life-threatening and time-sensitive conditions. In most of these kind of critical situations, AI can help us better diagnose problems easily and quickly so that we can make decisions easily and act quickly.

Impact of AI in Infectious Diseases

Though Coronavirus or COVID-19 trends the newscast, these kind of infectious diseases or outbreaks aren't something new for the humanity and it has faced several throughout history. In recent years, infectious diseases are more accountable with high percentile in healthcare expenditures, appreciably impacting the health of individuals and societal communities.



Before COVID-19, three major outbreaks were documented: Ebola(2014-2016) reported 28,646 cases, SARS(2002-2004) reported with 8098 cases and MERS(2012) reported with 2494 cases. Based on the documentation of parasitic infectious diseases over 3.9 million hospital outpatient-department got visited in 2011 and in 2014, for the same reason over 17.8 million people visited physicians in their respective offices. In 2014, many other illness were documented with new cases which includes



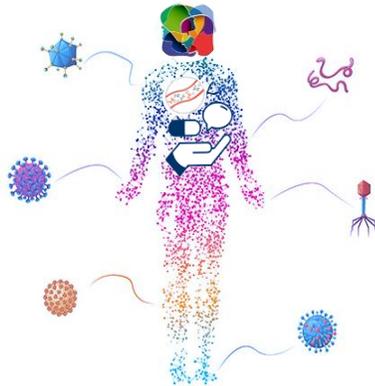
Dr. R. Elakkiya is currently working as Assistant Professor in Department of Computer Science & Engineering, School of Computing, SASTRA University, Thanjavur. She has 8 years of extensive research experience in the field of Artificial Intelligence & Machine Learning and she is very much passionate towards the recognition of Sign Languages of different countries. Apart from Sign Language Recognition, remarkable contributions has been made in the field of medical image processing in early diagnostics of cervical cancer using colposcopy images, epilepsy seizure prediction using EEG signals and COVID-19 using Chest Xrays and CT Scan images. Her research specifically focusses on addressing the trending issues and huge need for ML & DL, by filling a gap within a multidisciplinary field to include computer science, mathematics, engineering, and alike application domains. She is presently the Editorial Board Member in Information Engineering and Applied Computing Journal and reviewer to many top tier journals. She can be reached at elakkiya@cse.sastra.edu

Tuberculosis(9,421 cases), Salmonella cases (51,455 cases), Lyme disease (33,461 cases) and meningococcal disease (433 cases)¹.

Researchers now started to use AI to pinpoint the environmental and epidemiological issues that paves way for epidemics and to predict the infectious disease outbreaks earlier before they materialize. A team of US researchers from USC Viterbi School of Engineering developed an AI algorithm to help decision makers to cut down the overall community transmission of tuberculosis (TB), malaria and gonorrhoea diseases.

Based on simulation results from the computers, the researchers validated their algorithm on two real-time diseases: TB data from India and gonorrhoea data from United States. From the results, they inferred that the algorithm did a superior work in reducing disease cases by sharing the needful information about these diseases with individuals who are at risk.

Microsoft, using AI are partnering with Adaptive Biotechnologies to assist in the bioinformatics analysis of DNA sequencing by decoding the T-cell and B-cell receptors to assess the human immune system. The utmost objective of their analysis is to create a universal blood test to detect variety of diseases including infectious diseases in very early stage of transmission by reading the person's immune system. This epitomises the power of AI for



accompanying the human factor and recent trends in technologies at its fullest and best.

AI & COVID 19-The World Pandemic

Coronavirus or COVID-19 which was first identified in Wuhan, China is now a world pandemic. On 10th June 2020, World Health Organization (WHO) declared COVID-19 has its spread over 216 countries or territories or areas and so far the deadly virus infected more than 71.4 million people and has claimed more than 4 million lives globally.

The better we trace, the better we fight against this highly contagious disease. AI paves it's way here to learn and detect an outbreak of COVID-19. Blue Dot, a Canadian health monitoring platform raise the first alarm about the novel coronavirus infections to the world. BlueDot's AI forecasted the prediction of spread and warned about the issue and risk several days before the public warnings released by Centers for Disease Control and Prevention and World Health Organization. SenseTime used AI technology for face recognition to identify the people and detect their body temperature to check for the

symptoms of fever and they have deployed the face and temperature detection software in China's sophisticated surveillance system.

Radio-Imaging departments in healthcare conveniences are being charged with the amplified load created by the virus. AI-powered diagnostic tool using chest xrays was

AI HAS ITS VAST ABILITY TO RAPIDLY TRACK, DIAGNOSE AND MANAGE VARIOUS INFECTIOUS DISEASES IN REAL TIME.

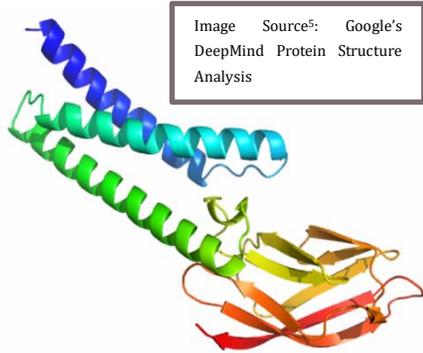
developed by various researchers across different institutions in India^[2,3] to reduce the burden of RT-PCR test. Alibaba, Chinese e-

commerce organization built a diagnostic tool using CT scan images and their claim states 96% accuracy in diagnosing the virus in seconds. Another researcher from IIT-Hyderabad^[4] developed a test kit costs only ₹600 per test which is 10% of actual cost of RT-PCR test. The test kit is powered by AI technology which would give the results in just 20 minutes thereby it can break the another barrier in diagnosing the infectious diseases.

To understand the protein structure of COVID-19 virus, Google's Deep Mind⁵ division used AI and its advanced computing power to help others develop treatments for the cause. BenevolentAI uses AI to build drugs to treat coronavirus. AI based Chatbots in Whatsapp, MyGov Corona helpdesk launched by Ministry of

Health, Government of India have been useful in creating the awareness about the infectious disease and communicating the essential information to the people and can make the people getting free online health consultation services through it. Government of India launched Arogya Setu, an AI based application for smartphone's users to provide the information about novel coronavirus infection using GPS system and Bluetooth technology that will help user to know how far they are from the infected person.

The extended use of AI and machine learning has enabled



researchers, start-ups, organizations and governments to prevent or better reduce the harm and disruption of infectious diseases. AI has its vast ability to rapidly track, diagnose and manage various infectious diseases in real time. AI not only will assist in developing better algorithms or models for tracking the transmission, forecasting the spread and diagnosing the diseases, but might also be influential in thwarting untimely deceases.

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Image Source²: Chest X-ray Classification

MRI FOR IMAGING INFECTIOUS DISEASES

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Of all the imaging modalities currently available for clinical diagnostic needs and research evaluation Magnetic resonance imaging (MRI) holds a very special role in being highly accurate and anatomically precise in its capabilities. MRI uses the inherent magnetic properties of the abundantly available hydrogen proton in the human body at all anatomical levels and hence is

radiation free which has been in many instances the shortcoming of other radiological imaging techniques.

The role of MRI in the setting of brain stroke,

musculoskeletal imaging, brain and spine imaging, cardiac imaging and neurodegenerative disorder evaluation has become essential and pivotal over the past decade without any competition and is only limited by the amount of time required for acquiring and interpreting the scans. There has been substantial paradigm

shift in the utilization of MRI capabilities from just being a tool of anatomical imaging to physiological imaging by assessing the response of body to injection of drugs or contrast agent, to functional imaging of body like in thinking processes or beating heart or CSF flow or bowel movement assessment or kinematic imaging of joints, to the latest Molecular

THE ROLE OF MRI IN THE EVALUATION OF INFECTION WAS MORE OF A CONTRIBUTORY ROLE IN PREDICTING A POSSIBILITY RATHER THAN CONFIRMATORY OR COMPLETELY DIAGNOSTIC

imaging by non-invasively assessing cellular and molecular processes through convergence of engineering, molecular biology, chemistry, immunology, genetics and image analysis.

Though traditionally nuclear medicine imaging techniques using tracers in ¹⁸F FDG-PET or SPECT has been the mainstay in Molecular imaging particularly because of low sensitivity of MRI contrast agents, there have been significant developments in the role of radiation free imaging using



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USG or MRI in the recent years. Molecular MRI imaging contrast agents are usually based on nanoparticulate probes which contain a high payload of contrast generating materials like iron oxide nanoparticles

or nanoscaffolds loaded with gadolinium chelates.

The role of MRI in the evaluation of infection was more of a contributory role in predicting a possibility rather than confirmatory or completely diagnostic, however, unsurpassed information is made available in defining the exact extent, nature and involvement of anatomical structures involved through infective disease processes by its excellent inherent in-depth intrinsic soft tissue contrast and higher-level detailed anatomical resolution imaging. It still has no role or very limited role in directly or accurately detecting the infectious agent responsible for disease and requires very good interpretation skills from dedicated experienced radiologists to precisely make a particular infective agent as causative. However, there has been a substantial improvement in the interpretation skills of radiologists of all experiences in characterizing the lesions as possible bacterial or fungal or parasitic or viral etiologies in many instances.

MRI has made significant inroads into the evaluation of chemical and pathological composition of the infective and non-infective disease processes which has been an imaging challenge to-date through various advanced and refined techniques like diffusion imaging / angiography / spectroscopy / arterial spin labelling / perfusion / diffusion tensor imaging / magnetization transfer and T1

weighted positive contrast imaging using lanthanide chelates like Gadolinium or non-lanthanide paramagnetic Manganese based contrast agents. MRI is also in a position to determine the time frame of the infection process in the body with reliable assessment of acute or chronic status of the disease which has been in many instances difficult to interpret even at intra operative assessment.

MRI is the investigation of choice in evaluating cerebral and spinal infections at various anatomical levels - be it at skull level or brain coverings or brain fluid - CSF or nerves coming out of brain or within brain parenchyma or spinal cord which is poorly evaluated by Computed Tomography (CT) or ^{18}F FDG-PET. The MR imaging characteristics have been so overwhelmingly uniform in predicting the causative infective agent indirectly in certain common diseases like tuberculosis, cysticercosis, toxoplasmosis, cytomegalovirus encephalitis or syphilis, aspergillosis, cryptococcosis or herpes or HIV that they just need correlative lab testing or specific targeted culture or simple microbiological investigations for validation. Though motion related artifacts have been a major constraint in evaluation of moving structures like heart and abdomen through MRI, the use of ECG and respiratory gating techniques have successfully targeted the acquisition only to non-mobile phases and led to improved

interpretation in infective disease processes like abscess in liver or spleen or kidney where it is key to differentiate infection vs neoplastic nature of lesion. Functional parameterization and impairment related to infectious diseases are being evaluated in dynamic cardiac MRI studies.

Recently experimental Molecular imaging technologies have been used to image invasive pulmonary aspergillosis using antibody-guided PET/MRI not just for cerebral or central nervous system infections but also for pulmonary infections using ultra-short echo times (Thornton CR et al., 2018). Recent studies have also demonstrated the enormous potential of antibody-guided PET/MRI technologies to dramatically improve the molecular imaging of viral (Santangelo et al., 2014), bacterial (Wieher et al., 2016) and fungal (Rolle et al., 2016, Davies et al., 2017) infections in vivo, with the real possibility of precision medicine for infectious diseases in the near future (Jain, 2017).

Future promise

The use of superparamagnetic iron oxide (SPIO) nanoparticles with their characteristic magnetic susceptibility qualities and their ability to be labeled to macrophages and subsequent MRI detection / trackability has been used to evaluate infectious diseases and their immune system interactions. SPIO use T2-weighted imaging with negative contrast and are coated with

dextran (Feridex), starch, polymer (monodisperse iron oxide nanoparticles-MION) or citrate or inorganic silicon materials or polyacrylic acid or dopamine or deferoxamine and the recent being USPIO (Ultrasmall super paramagnetic iron oxide) and CLIO (cross linked iron oxide).

While most of the clinical MR imaging uses the water protons ^1H to create contrast enhancement, nanoparticle imaging using ^{19}F is being used for research purposes due to its high gyromagnetic ratio and low abundance in the body which results in absence of undesired tissue

background signal. Role of other Functional MRI approaches, including spectroscopic imaging of MRI-visible but less sensitive heteronuclei, such as ^{31}P or ^{13}C is also looked into. Particularly the role of MRI at image analysis and drug development, Fusion of dynamic MR & dynamic ^{18}F FDG-PET for parametric (PK) maps and cancer typing is looked into in the current research protocols. Labelling of the influenza A/Udorn/307/1972 virus (H3N2) with the MRI agent, 5-fluorotryptophan, demonstrated the feasibility of using (^{19}F) MRI to directly visualize and quantify the helix-helix ED dimer interface of NS1A protein in

influenza virus infection (Aramini JM et al., 2014).

There is a lot of exciting promise for collaborative imaging using novel MRI imaging techniques, high strength MRI imaging, nanoparticle contrast molecular imaging and immunoPET imaging in animal studies relevant not just to infectious diseases but also for cancer disease and the scope for subsequent validation with approval in human imaging for better management of human diseases and well-being.



Upcoming Event.....

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PHOTOACOUSTIC MOLECULAR IMAGING OF INFECTIOUS DISEASES

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Significance

Infectious diseases are caused by pathogens such as bacteria, viruses, fungi and parasites. Among all human diseases, infectious diseases cause high mortality, morbidity and financial burden [1]. It is estimated that by 2050, antimicrobial drug resistant infections will become the leading

cause of mortality globally, 10 million per year, surpassing the number of cancer deaths. The current COVID-19 pandemic

exemplifies the need for rapid development and testing of cost-effective diagnostics, various short-term remedies and preventive vaccine.

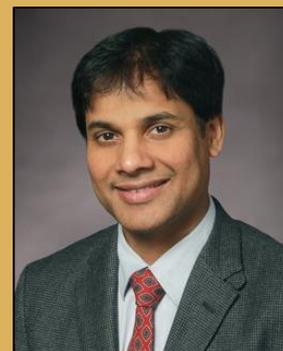
Current technologies and the gap in the knowledge

In vitro diagnostic methods for infectious diseases, although gold standard, suffer from disadvantages such as invasive tissue sampling (e.g., nasal swab or blood) with risk of contamination, static one time-point

measurements, and also time consuming. For example, it takes up to 2 days to diagnose the Covid-19 disease using a standard SARS-Cov-2 virus-specific reverse transcriptase polymerase chain reaction (RT-PCR) test [2]. Serial testing is often required to rule out the possibility of negative results.

days) information of the disease progression using non-invasive approaches. For example, pneumonia (lung infection with fluid and pus accumulation) is one of the main symptoms of the mid-phase of the infectious diseases.

Anatomical imaging modalities such as chest computed tomography (CT) and lung ultrasound (LUS) play a key role in serial testing of pneumonia and rule out the possibility of false negative



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results. However, for early diagnosis of the disease and for developing, testing and translating various treatment options through pre-clinical phase, pathogen-specific molecular imaging technologies are required. Molecular

NON-IONIZING, NON-
INVASIVE, PORTABLE, LOW-
COST, AND REAL-TIME
MOLECULAR IMAGING
TECHNOLOGIES ARE DESIRED
TO SHIFT THE PARADIGM OF
INFECTIOUS DISEASE
DIAGNOSIS AND TREATMENT

Medical imaging technologies provide spatial (whole body or organ specific) and temporal (several

imaging can help delineate the inflammation from infection, identify infectious pathogen, and follow the pathogenesis in real-time. Positron emission tomography (PET) is the most sensitive whole-body molecular imaging technology widely used in several pre-clinical and clinical applications of cancer and neurological diseases. Recently, the potential of radioactive PET tracers for imaging infectious diseases caused by bacteria, fungi and viruses have been demonstrated in pre-clinical as well as pilot clinical studies [3]. Although PET offers exciting possibilities for studying pathogenesis in pre-clinical infectious disease models, like CT, it is not ideal for repeated testing on patients due to the use of ionizing radiation. Moreover, PET imaging needs special access to cyclotrons for isotope production, preferably isotopes with longer half-life to sustain remote distance applications, and experienced radiochemists for molecular probe development. Further CT, PET and magnetic resonance imaging (MRI) are expensive and bulky instruments, and hence not suitable for widespread use in the remote parts of the world [4]. Non-ionizing, non-invasive, portable, low-cost, and real-time molecular imaging technologies are desired to shift the paradigm of infectious disease diagnosis and treatment.

Photoacoustic Imaging (PAI) is a hybrid optical-ultrasound technique that provides optical absorption based molecular- and functional- contrast

images of deep tissue with high ultrasonic spatial resolution [5]. In PAI, pulsed photoexcitation of the tissue and subsequent thermoelastic expansion of light absorbing chromophores (e.g., oxyhemoglobin, deoxyhemoglobin, melanin, and lipids) leads to broadband ultrasound wave generation. This photoacoustic effect is analogous to the thunder caused by lightning. For molecular mapping, spectroscopic PAI uses multi-wavelength tissue excitation to excite molecules at their resonance peaks in the absorption spectrum. Conventional ultrasound detectors placed outside the body detect these wavelength specific photoacoustic waves and form high contrast images in real-time at ultrasonic resolution. Spectral unmixing algorithms are used to map the distribution of different molecules inside the tissue. Imaging depth and spatial resolution are both scalable using ultrasound and optical parameters; typically, a micron resolution at 1 mm depth and a sub-mm resolution at 5 cm depth. Over the past two decades, PAI has evolved as a multi-scale imaging technology, enabling *in vivo* imaging from organelles to organs in pre-clinical and clinical translation applications. Strong intrinsic optical absorption from oxyhemoglobin and deoxyhemoglobin molecules enabled label-free PAI of blood vasculature, associated angiogenesis, oxygen saturation, and total hemoglobin concentration (blood volume). This multiparametric vascular information

allowed unrivaled pre-clinical PAI applications in cancer (tumor angiogenesis and hypoxia measurements), cardiovascular (thrombosis and plaque lipids) and neuroscience (cerebral blood flow and oxygen saturation). Label-free vascular imaging capabilities of PAI were also demonstrated in clinical applications such as breast angiography [6], Crohn's disease [7], and more recently transrectal prostate imaging [8]. Further, when powered by externally administered photoacoustic molecular agents, the sensitivity and specificity of PAI can be further enhanced, and its applications can be largely extended from tissue level to molecular and cellular levels. For this purpose, a wide variety of photoacoustic contrast agents, from small molecules to organic and inorganic nanoparticles, have been functionalized to target disease specific biomarkers. In principle, all light absorbing fluorescent molecules have certain probability to generate photoacoustic signal when relaxing to the ground state through competing non-radiative heat decay. Several targeting approaches have been reported in pre-clinical PAI applications using fluorescent molecules (e.g., Indocyanine green and IR800-dye) and nanoparticles (gold, carbon nanotubes, liposomes). This includes photoacoustic reporter genes (such as iRFP) [9], antibodies (e.g., anti-integrin) [10], enzyme (e.g., matrix metalloproteinases (MMPs) and Furin) activatable agents [11-12], and

DNA aptamers [13]. Similar to fluorodeoxyglucose (FDG)-PET tracer (^{18}F -FDG), a fluorescent glucose analogue, 2-deoxy-2-[N-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)amino]-D-glucopyranose (2-NBDG) is capable of crossing the blood-brain-barrier (BBB) via glucose transport protein GLUT, and was demonstrated to map brain metabolism in mouse models [14]. These pre-clinical studies demonstrate the potential of photoacoustic molecular imaging for targeting infectious pathogens.

On the other hand, the PAI scanners for both pre-clinical and clinical applications are undergoing rapid developments. Since ultrasound and photoacoustic technologies share the same ultrasound detection platform, the state-of-art scanners are capable of simultaneously displaying ultrasound based anatomical information and photoacoustic based functional and molecular information of the tissue. This is similar to combined PET+CT or PET+MRI scanners, where PET provides molecular information, CT provides anatomical information, and MRI provides soft tissue contrast. In contrast to these conventional systems, dual-modality photoacoustic and ultrasound (PAUS) scanners are portable (integrated into a cart) and are cost-effective in the price range of \$80,000 to \$800,000. While dedicated small animal PAUS scanners can image whole mouse, clinical PAUS scanners (developed by integrating PAI capabilities to commercial US

scanners) are limited to imaging organs. The advent of micromachined ultrasound transducers, miniaturized optical sources (e.g., laser diodes), field-programmable grid array (FPGA) based data acquisition, and deep learning algorithms are helping further reduce the footprint and the cost of PAUS scanners [15]. In future, a smart integration of these multidisciplinary technological advances will likely achieve a wearable and portable PAUS imaging system suitable for diagnosing infectious diseases in remote parts of the world.

Potential impact of photoacoustic molecular imaging for infectious disease

To reliably image pathogens and understand the pathogenesis, the imaging technology should be sensitive to unique pathological hallmarks and/or molecular biomarkers of the pathogens. Besides diagnosis, prognostic information extracted from the imaging biomarkers (e.g., pulmonary aspergillosis) may also improve the infectious disease treatment and management, and therefore also likely help reduce the health care cost. PAUS imaging scanners integrated with anatomical, functional, and molecular imaging capabilities can play a critical role in the three key areas of the infectious disease: 1) pathogen-specific diagnosis, 2) understanding pathogenesis and 3) optimize treatment options.

1. Pathogen-specific diagnosis

Like in the case of PET, different photoacoustic molecular targeting approaches can be employed to detect infectious pathogens. For imaging bacterial infections, the key challenge is that the molecular probe should have high binding affinity to bind and accumulate to bacterial cells and should be able to distinguish bacterial cells from host mammalian cells. To overcome this, photoacoustic molecular probes must be capable of targeting multiple binding sites on the bacterial cell wall or a metabolic substrate trapped by the bacteria induced enzyme activity. For example, a fluorescent derivative of maltotriose (Cy7-1-maltotriose), which provides both fluorescence and photoacoustic contrasts, was demonstrated to detect infection, assess infection burden, and determine the efficacy of antibiotic treatment in *E. coli*-induced myositis and in a clinically relevant *S. aureus* would infection murine model [16]. For imaging viruses, which are much smaller than bacteria, photoacoustic reporter genes or molecular probes that activate in the presence of virus induced enzymes may yield better results. For example, a luciferase and fluorescent fusion reporter strategy for influenza virus was demonstrated in mouse models. Both bioluminescence and fluorescence imaging were used to follow the influenza virus as it traffics to the lungs and cause lung infection. However, both bioluminescence and fluorescence imaging cannot provide information about the other infections

and inflammation caused by the virus. Dual-modality PAUS scanners can not only track the influenza virus using the above fusion reporter but also can image lung infection in the ultrasound mode, and local tissue inflammation using the functional hypoxia measurements in photoacoustic mode.

Emerging literature on PET imaging of other virus types, ⁸⁹Zr-VRC01 antibody targeting HIV and ⁶⁴Cu-743 Ab targeting Semian Virus, shows that targeting viral envelop proteins using antibodies is an attractive approach to image viruses. Alternatively, enzymatic kinases have also be targeted for PET imaging of viruses, such as Thymidine kinase in HSV-1 virus and protein kinases in Cytomegalovirus (CMV), using specific inhibitors. As in the past, these PET targeting strategies can be adapted to develop photoacoustic molecular probes capable of detecting different viruses, including coronavirus 2 (SARS-CoV-2).

2. Pathogenesis

Beyond diagnosis, PAUS scanners can be used to further understand the pathogenesis of infectious diseases in pre-clinical models by imaging the host immune response and also treatment response. Liquid or solid tissue biopsy cannot provide complete information about the spatial and temporal heterogeneity of the disease and the disease burden. Small animal PAUS scanners can provide non-invasive imaging of deep-seated infections, inflammation, and immune responses in mouse models of

infectious disease. Lung infections can be imaged using ultrasound, inflammation affecting blood oxygen saturation at infectious site can be measured using photoacoustics, and it was also demonstrated that the immune response in mouse models of bacterial infection can be imaged by intravenously injecting T Cells labeled with fluorescent molecules (e.g., NIR-797-isothiocyanate) [17]. This study showed time activity of T-cells gradually decreased at the bacterial infection site and lymph nodes.

3. Treatment planning

PAUS imaging can help identify suitable antimicrobial treatments, follow response to treatments, and help vaccine development. For example, it is very important to understand different mechanisms of action of a specific vaccine. Photoacoustic imaging markers that specifically target immune cell subsets can help identify the changes due to vaccine in the same animal over a period of time, providing multiple readouts on a single individual.

In summary, dual-modality PAUS scanners integrated with suitable molecular imaging strategies are capable of providing complementary anatomical, functional and pathogen-specific molecular information. Rapid developments in PAUS instrumentation, clinically relevant contrast agents and molecular probes offers exciting promise for diagnosing and treating infectious diseases.

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Interesting snippets - Milestones in medical imaging #3



Discovery	Year
Digital radiography introduced	1978
MRI	1980
3D image processing for diagnosis	1984
PET scanning	1985
Spiral CT, MR angiography	1989
EPI, Open MRI	1993
Artificial Intelligence in image processing	Current trend



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KNOW A TECHNIQUE SERIES

ROLE OF FLUORESCENCE IN-SITU HYBRIDIZATION (FISH) TESTING IN MOLECULAR GENOMICS

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Gautam Bulusu. BS

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Introduction

Molecular diagnostic assays are rapidly expanding areas providing results with high sensitivity and specificity. The newer molecular techniques such as fluorescence in situ hybridization (FISH) has profoundly changed the field of molecular diagnostics. FISH is a test that "maps" the genetic material and can be used to visualize specific genes or portions of genes. Due to recent advancements, this technique has found increased application in many areas, such as cytogenetics, prenatal diagnosis, cancer research & diagnostics, gene loss and/or amplification, gene mapping, and identification of microbiological pathogens. The availability of different types of

probes and the increasing variety of FISH techniques has made it widespread and diversely applied technology.

Methodology

FISH assists researchers or clinicians to identify where a particular gene is located within the chromosomes. The initial step of the FISH technique is to prepare short sequences of single-stranded DNA that match a portion of the gene the researcher is looking for called "probes". Following this step, these probes are labeled by attaching

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REVOLUTIONIZED
MOLECULAR GENOMICS
IN RECENT TIMES, THUS
ESTABLISHING A
POWERFUL TOOL IN
PATIENT CARE.**

one of many available colors of fluorescent dye. Because DNA is composed of two

complementary strands that bind



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tightly together, these single-stranded probes will bind to each complementary DNA strand. When a probe binds to a chromosome, its fluorescent tag provides its localization and interpretation.

Applications

FISH testing is widely utilized in oncology, cytogenetic and microbiology settings, such as breast cancer, hematological, and other hereditary cancers. In breast cancer

patients the tumor tissue removed during a biopsy is subjected for FISH testing to check for extra copies of the *HER2* gene. The higher the number of *HER2* gene copies, the more *HER2* receptors there are on the tumor cells, which subsequently stimulate the growth of breast cancer cells. FISH test results give information on cancer as either "positive" or "negative" (Figure 1 and Figure 2). A "positive" *HER2* result by FISH method, the tumor more likely respond to treatment with trastuzumab (Herceptin), a drug that blocks the ability of *HER2* receptors to receive growth signals. Many clinical trials use cytogenetic and FISH data to stratify patients according to specific risk factors. FISH is often used as a

stand-alone technique for investigating abnormalities and following-up on patients. This, alongside its relatively low expense, makes it a very convenient investigative tool.

Among the rapidly developing alternative techniques, FISH serves as a bridging technology between microscopy and traditional microbial culture methods in the identification of microbial pathogens routinely in laboratories. FISH technique uses short fluorescence-labeled DNA or nucleic acid-mimicking peptide probes (PNA probes) to identify microbial organisms. The PNA FISH probes provide a rapid and accurate diagnosis of infectious diseases. This makes

them well suited for the routine application and enabling of clinical microbiology laboratories to report important information for patient therapy within a short turn around time (TAT). FISH PNA probes represent a new generation of therapy-directing diagnostics.

Conclusions

FISH technique has advanced allowing screening of whole genomes through multi-color chromosome probes using comparative genomic hybridization (CGH) method. This simple yet effective technique has revolutionized molecular genomics in recent times, thus establishing a powerful tool in patient care.



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Dr. M. G. Ramakrishna Rajan is an outstanding scientist who headed the Radiation Medicine Centre, Bhabha Atomic Research Centre, Government of India till June 2016. He was also a DAE-Raja Ramanna Fellow till December 2019 and a Professor at the Homi Bhabha National Institute. Dr. Rajan completed his Master of Science (Chemistry) from Bangalore in 1975 and trained in BARC Training School in the 21st batch of Chemistry in 1977-1978. He went to do a Diploma in Computer Management in 1982. He obtained his Ph.D. in Applied Biology in 1993 from Mumbai University. He specialized in Medical Cyclotron and PET Radiopharmaceuticals and focused on Radioimmunoassay, Chemiluminescence & Related Methods.

Dr. Rajan has extensive experience in development of diagnostic assays for various infectious and non-infectious conditions. He was involved in developing immunoassays in the Department of Chemical Pathology at Guys Hospital, London where he worked on malaria detection. He also worked towards development of free thyroid hormone assays at the Department of Molecular Endocrinology, Middlesex Hospital Medical School, London in 1984 where he worked with Prof. R.P. Ekins. He has vast experience in the chemistry of the production of ^{18}F FDG, its quality control, aseptic dispensing, etc., during his tenure at Bereich Zyklotron und Radiopharmazie of the Universitätsklinikum Hamburg-Eppendorf, Germany in 2003.

Dr. Rajan was also the Deputy Chief Executive for BRIT. He has guided personnel in the operation of the Medical Cyclotron for the production of PET-radiopharmaceuticals assisting with installation, commissioning and operation, from 2002 to 2016. From this facility, over 5000 batches of ^{18}F -FDG have been produced during this period under cGMP guidelines and supplied to hospitals in Mumbai and Pune. Other ^{18}F -Radiopharmaceuticals, viz ^{18}F NaF, ^{18}F FMISO, ^{18}F -FLT, ^{18}F -FET were also prepared for diagnosis and research purposes during his tenure. His laboratory has actively carried out testing of thyroid functions for more than 14000 samples a year. He has guided Ph.D. students in the fields of Chemistry and Life sciences. He was a Member of Expert Committee for Indian Pharmacopoeia Commission, New Delhi, and also the Member of various Regulatory Committees in BARC and AERB. He worked as an IAEA Expert for training staff in developing countries and was also an IAEA consultant for several Coordinated Research Programs. He chaired AERB Committee to bring out a guide for Medical Cyclotron Facilities. He has published 62 research articles and book chapters. He is a life-member of MISI and has constantly encouraged all scientific endeavours of MISI. We appreciate his immense contributions to the field of diagnostics and radiopharmaceuticals in India and hope that he will continue to motivate and inspire youngsters in these domains.



YOUNG PROFESSIONAL COLUMN

IMAGING - A TORCH IN THE DARK

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Generally, imaging refers to the visual reproduction of an object of interest. It is a wonderful technique that gives a deep insight to the valuable details. One such technique is the “**Photography**” where the moments are cherished forever. This word is coined by Sir John Herschel in

1839 derived from Greek where ‘Phos’ means light and ‘graphe’ means either drawing or writing. Therefore, it

means drawing with light. In the similar lines, researchers worldwide were engaged to utilize it for medical purpose where, an excellent patient compliance with painless and easy procedures eliminating the associated surgical complications can be made possible. Currently, an array of techniques are available to the ailing community of people. Few of the

notable imaging techniques are X-ray, computer tomography (CT), nuclear medicine scan, magnetic resonance imaging (MRI) and ultrasound.

In the present situation, a newly emerged virus from the family of beta CoV, SARS-CoV-2, has caused

an outbreak since December 2019. This pandemic has caused an unimaginable situation of lockdown and thereby, shattering the layman life and affecting the

entire world economy. The moral which have been learnt is that the early detection is the hi-time need of the day. According to the reports submitted by various countries world-wide, reverse transcriptase RT-PCR should only be utilized to detect the virus in the swab sample, collected from suspected person’s throat. But, Paras Lakhani, MD, an associate



Dr. Sakthivel Gandhi completed his Ph.D. from SASTRA Deemed University, Thanjavur, India with research focus on hybrid materials for theranostics applications. He has won the best dissertation award from SASTRA. He had his postdoc training in the Department of Basic Science at Changwon National University, Republic of Korea. He joined SASTRA as Assistant Professor in December 2012. He is the reviewer for funding agencies, like RSCF (Russian Science Foundation). He received the core research grant from Department of Science & Technology. The research goal of Sakthivel Gandhi, group leader of hybrid materials laboratory is to create an efficient optical and electrochemical diagnostic tool in addition to the development of materials for PDT, PTT and sensor applications. He can be reached at sakthivel@scbt.sastra.edu

professor of radiology at Thomas Jefferson University Hospitals in Philadelphia says, “Sometimes the RT-PCR test is negative early in the disease course, but the chest CT is positive for

findings that could represent coronavirus infection." Hence, the imaging techniques will be considered as the pillars in screening of pandemic diseases in near future.

On the other hand, a study published in Science concludes that using cryo electron microscope (CryoEM), can elucidate the structure of

spike (S) glycoprotein of SARS-CoV-2. It is well known that the structure of protein plays a key role in the development of vaccines, therapeutic antibodies, and diagnostics and hence, establishing their importance of imaging in the field of diagnosis and therapy.

In addition to the imaging techniques, the associated materials such as contrast agents, photodynamic agents and photothermal agents, play an important role, as if the work done by the machine and the associated materials are equally shared. At times, more efficiency is possible only in the presence of associated materials. After the invention of scanning tunnelling microscope (STM), the development of new class of synthetic nanoparticles (SNPs) have been initiated in large scale. SNPs, whose size ranges between 1 and 100 nm, are emerging as multipurpose tools in biomedical applications, and specifically in

biomedical imaging. Their amicable features namely the modifiable surface functionality, high surface area, superparamagnetic property and the tuneable optical properties, make

and absence of surface functional groups, have been overcome by these above-mentioned surface modifications. Especially the silica encapsulation provides, biologically

inert nature to the UCNPs along with tailored surface. The modified surface can be easily accessed by the receptors or specific sites of diseased region, whereas the porous nature of silica shell can host drugs or photothermal agent or photosensitizers within. Now, the exposure of NIR

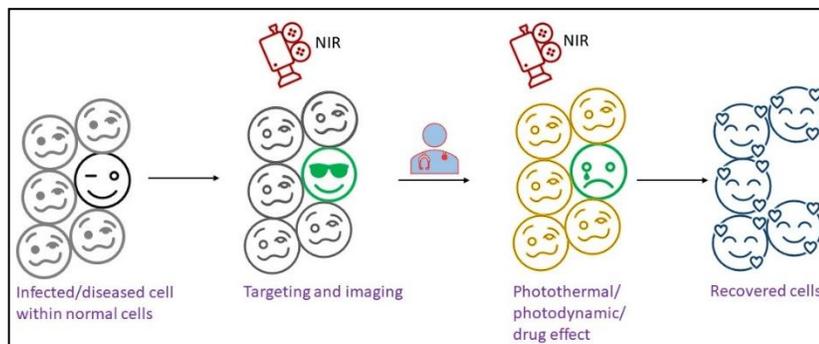


Figure 1: Pictorial representation of treating infected/diseased cells through PDT/PTT/targeted drug delivery, using UCNPs.

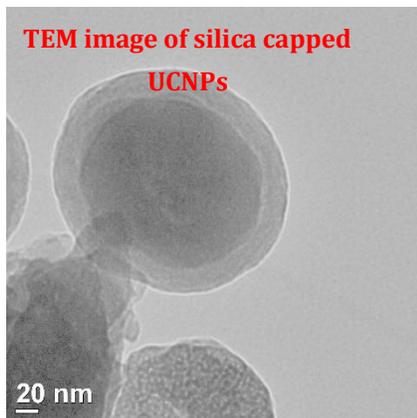
SNPs as the potential probes for early detection and cure of deadly diseases such as cancer through MRI, CT, PDT (photodynamic therapy) and PTT (Photothermal therapy). Among the various nanoparticles, rare-earth elements introduced upconversion nanoparticles (UCNPs) have been gaining lot of attention in multimodal imaging area due to their ability to convert the lower energy near infrared light to higher energy visible light. In addition to optical and magnetic imaging which are used for diagnosis purpose, UCNPs are actively incorporated to treat diseases such as cancer through PDT and PTT.

Core-shell based UCNPs developed through amphiphilic coating, ligand exchange and silica encapsulation have made a breakthrough in nanomedicine and bioimaging fields. The limitations of blank UCNPs such as toxicity, aggregation, hydrophobicity

helps UCNPs to get excited and upconvert the radiation into visible light. The visible light would either, be taken to heat-up the region by using photothermal agent or to produce ROS by using photosensitizers. Overall, the tracking would be possible using UCNPs through two different ways namely, optical and magnetic. The higher penetration of NIR can easily reach UCNPs inside the body and it can be successfully utilized under *in-vivo* condition. Additionally, the presence of magnetic Gd^{3+} based substances in UCNPs can be tapped for imaging under MRI.

Apart from therapy, other areas of research drawing attention of researchers, are two hot topics namely multimodal imaging and diagnosis. These topics not only boost up the career of researchers but, also to come out with a reliable product beneficial for the society. Among the various nanomaterials, once again core-shell

based UCNPs are highly sorted owing to their versatility in diagnosis and imaging solutions for several ailments viz., different types of cancers, viral and bacterial diseases. This can be attributed to their inherent optical behaviour. The current pandemic situation has necessitated the development of a 'point of care' based on-spot detection of disease. Because the isolation of diseased, can avoid the social spread alone. At present the anti-body and aptamers based lateral flow sensing



system that utilizes UCNPs, has drawn a considerable insight. The kit made using antibody and aptamer along with NIR light would suffice for the early detection of disease. This is really a booming technology right now in biomedical field.

To conclude, imaging is a simple object detection method that is built on the basic principles of light which gives an enormous information and hence, it is considered as an active area of research for several years. According to George Barbastathis, MIT, USA,

“Imaging, in general, relies on optimization to arrive at solutions that simultaneously satisfy physical constraints, which are the laws of light propagation and scattering from matter, and prior knowledge, which are the types of objects and object shapes that are likely to be encountered in any particular situation”. Although, the term imaging is used in several fields, it sounds invaluable in science because most of the scientific inventions came to light after the establishment of the imaging techniques. Thus, the enormous power of the imaging technique has well-paved the way for many breakthrough discoveries in the field of biomedical imaging science.

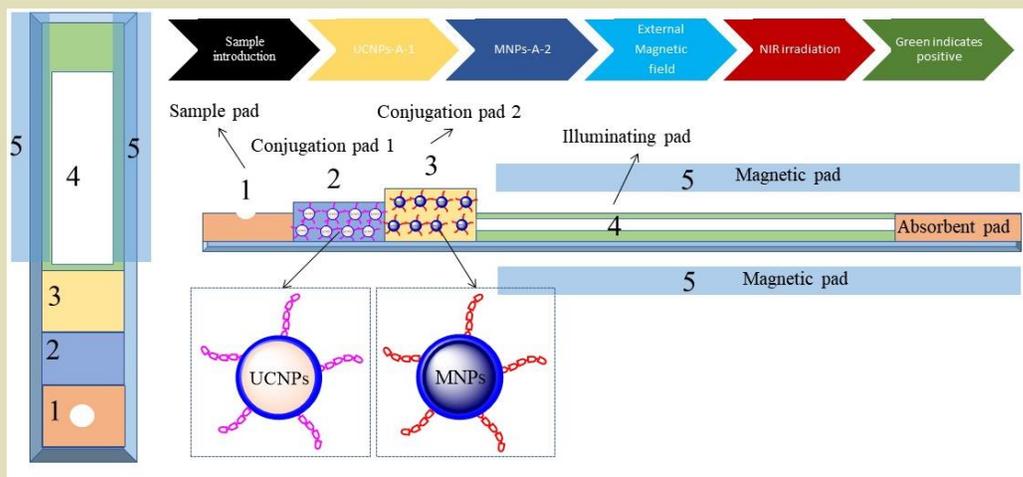


Figure 2: and pictorial representation of rapid kit for detecting SARS-CoV-2.

COVID-19 DIAGNOSIS & TREATMENT: WHERE DO WE STAND?

Prof. Uma Maheswari Krishnan

Dean, School of Arts, Science & Humanities, SASTRA Deemed University, Thanjavur, India

The emergence of a new viral strain in a marketplace in Wuhan, China in December 2019 has soon led to a global pandemic in a matter of weeks leaving over 4,50,000 dead and more than 93,00,000 infected as on June 22, 2020. The numbers continue to grow with fears of community

transmission looming large. India, with its high density of population is only behind US, Brazil and Russia in terms of number of infections. RT-PCR has been the gold standard for COVID-19 testing while few antibody-

WE ARE TRAPPED IN A COVIDIAN ERA WHERE ONLINE MEETINGS, MASKED FACES, ISOLATED SPACES, ECONOMIC CRUNCH, UNCERTAIN TIMES FOR RESEARCH IN TERMS OF MEETING DEADLINES AND FUNDING, AND MENTAL STRESS, HAVE BECOME OUR NEW NORMAL!

based kits are also in use for detecting the presence of SARS-nCoV2, the causative organism of COVID-19. There are several challenges in the diagnosis of COVID-19 that have been highlighted by experts. Apart from

being expensive, the design of an antibody against a virus that continues to evolve by mutating frequently resulting in different strains, makes it difficult to employ antibody-based kits as a reliable diagnostic tool. The sampling for RT-PCR is also critical as swabs

may be inadequate if the viral load shed is low. Sputum samples are better for analysis of the presence of the virus. Image processing techniques in combination with artificial

intelligence are being explored as a mode of diagnosis using radiography, which has also been elaborated in this edition of the newsletter. However, techniques for rapid and reliable screening of large populations are



Uma is a Ph.D. in Chemistry and has post-doctoral experience at UT Southwestern Medical Centre, Dallas, USA. She works with nanostructures and carries out surface modification to tailor their properties for appropriate applications in therapy and diagnosis. Development of stimuli-responsive intelligent therapeutics and point-of-care devices for diagnosis of clinically relevant markers is a major focus of her research lab. Her group uses *in silico*, *in vitro*, 3D spheroids and *in vivo* studies to establish the efficacy of these nanomaterials for the intended application. Understanding molecular mechanisms of these nano-interventions and assessment of safety and efficacy using a combination of molecular, biochemical, electrophysiological, imaging and spectroscopic techniques, is also a component of the group's research activities. She has over 200 publications in this area. She is currently the Secretary of MISI. She can be reached at umakrishnan@sastra.edu

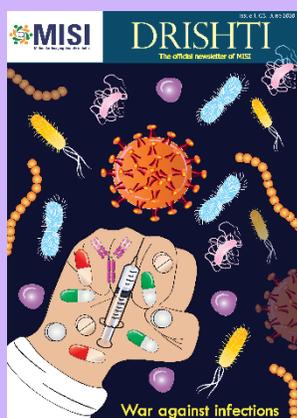
required to avoid the long and painful wait for results in isolation. Some interesting attempts such as a mask that changes color when it comes in to contact with the virus has been

reported, but cost and specificity issues limit their widespread use.

In the context of therapy, anti-inflammatory drugs like dexamethasone and anti-virals like remdesivir and favipiravir are being used to treat infected individuals. The usefulness of hydroxychloroquine is still mired in controversy. Several immune boosting formulations are being promoted as prophylactic measures though their potential in preventing COVID-19 is yet to be scientifically validated. While earlier

age and individuals with co-morbidities were considered to be at a greater mortality risk, there have been many cases, especially in India, where individuals below 45 have succumbed to COVID-19. Therefore, understanding the viral pathology is a key for designing therapeutic as well as diagnostic strategies. Asymptomatic individuals present another new challenge in diagnosing and treatment of this disease. Another dimension that is emerging is the implementation of social distancing and isolation that is

promoting mental stress and depression among individuals, which needs to be addressed. Overall, we are trapped in a COVIDian era where online meetings, masked faces, isolated spaces, economic strain, resource crunch, uncertain times for research in terms of meeting deadlines and funding, and mental stress, have become our new normal! In this scenario, it is essential for a knowledge network to develop solutions to tide over the current crisis.



About the cover image

War Against Infections!

Everyday we get exposed to new microbes and our immune system tries to neutralize them. Emerging techniques in science have aided researchers to develop synthetic drugs and vaccines that prove an important component of the arsenal in the war against infections. Imaging plays an important role in diagnosing the disease that helps in developing effective therapeutic strategies.



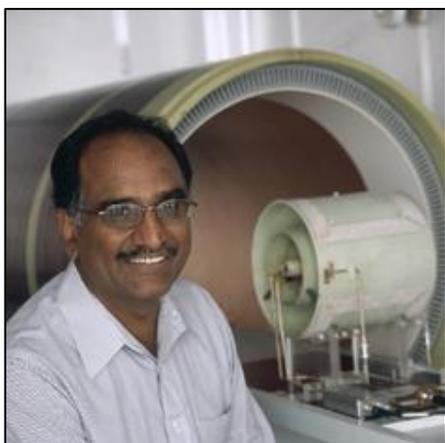
The cover art was designed and drawn by a young researcher Ms. V.S. Kaviarasi, a CSIR funded senior research fellow who uses confocal microscopy extensively to image samples from her research involving development of a theranostic nanosystem for management of cerebral ischemia.

FOCUS INTERVIEW

This section is devoted to interview with an expert who has contributed significantly to advances in molecular imaging. This quarter, our guest is Dr. Murali Krishna Cherukuri.

DR. MURALI KRISHNA CHERUKURI

Dr. MKC, a life member of MISI, is a senior investigator in the Radiation Biology Branch at the National Cancer Institute (NCI), USA. He also heads the Biophysical Spectroscopy Section. Dr. Krishna obtained his Ph.D. in physics from the Indian Institute of Technology, Madras, India, in 1984 and joined the NCI the same year. His research interests include studies of free radical processes in causing oxidative injury and antioxidant defense. He has also been involved in developing functional imaging tools to study tumor physiology. He can be reached at cherukum@mail.nih.gov



EPR at the same frequency, the magnetic field is 10 milliTesla. So the cost of EPR Imaging is significantly lower than that for MRI since magnets are easily manufactured at these fields. However since MRI uses ^1H from tissue water protons, no exogenous probes are needed. However for EPR imaging exogenous paramagnetic probes which are free radicals with simple spectra are needed. Recently available trityl radical probes with simple spectra and negligible toxicity at the doses needed for in vivo imaging, EPR imaging has become practical.

Q: Can you tell us briefly about your early academic journey?

A: I started my research career in the Physics department of IIT Madras in 1979 after a Masters in Physics. Initially I started my project on crystal growth but changed to studies of paramagnetism of transition metal ions such as nickel, copper, vanadium in single crystals using Electron Paramagnetic Spectroscopy. Though very basic research, it taught me the fundamentals of magnetic resonance spectroscopy.

Q: What was your early research centred on? What got you interested in free radical processes?

A: After I obtained my Ph. D in 1984, I joined as a post-doctoral fellow at the National Cancer Institute of the National Institutes of Health, Bethesda Maryland, USA. I was working in the Radiation Oncology Branch which is a clinical branch which also had significant laboratory research activities. Since radiotherapy involves free radicals in its therapeutic action and free radicals are paramagnetic, I was using EPR spectroscopy to study free radical intermediates in various radiolytic, photolytic and even chemotherapeutic drugs. This gave me exposure to tumor physiology and metabolism which helped me in my later years.

“The efficacy of radiotherapy depends on tumor oxygen status.”

Q: What imaging techniques are you using for free radicals?

A: EPR spectroscopy is the only technique which can image free radicals using magnetic field gradients similar to MRI. However, since the magnetic moment of electron is ~ 660 times stronger than ^1H which is used for MRI, at a given radiofrequency(RF), EPR imaging needs 660 times lower magnetic field. For example, if the RF used is 300 MHz, the magnetic field for ^1H based MRI is 7 Tesla whereas for

Oxygen molecule is paramagnetic with two unpaired electrons and can serve as a T2 contrast agent on the trityl radicals. Quantifying this contrast allows EPR imaging to map the tissue distribution of the trityl radical and monitoring the T2 contrast of tissue oxygen on the trityl radical allows mapping tissue oxygen.

Q: When do you think they can be used in clinical practice?

A: The efficacy of radiotherapy depends on tumor oxygen status. If the tumor has low oxygen levels, higher doses of radiation need to be used to treat effectively. EPR imaging is the only imaging method capable of generating quantitative maps of tumor oxygen. With this information, it is possible to develop radiation treatment planning to deliver appropriate doses. The trityl radical used for in vivo EPR imaging in pre-clinical research on experimental animals shows the promise of this technique. This molecule has already been used in humans at 25-50 times lower than used in animals in ¹³C MRI using hyperpolarized tracers to study tumor metabolism. If the sensitivity of detection can be improved it is a practical and inexpensive clinical imaging modality to study tumor physiology and tailor appropriate treatments.

Q: What are their advantages over current cancer imaging methods?

A: EPR Imaging provides quantitative maps of tissue oxygen. This is the unique feature of the method. This can be integrated with other MRI methods to comprehensively assess tumor physiology and metabolism.

Q: Where do you see free radical imaging in the management of cancer?

A: It is not possible to image endogenously generated free radicals. But using trityl radicals, EPR Imaging can obtain oxygen maps which can be used to tailor therapy.

Q: What will its role be in conjunction with current cancer imaging methods?

A: It will be useful along with PET and MRI.

Q: Will it have a role in drug development?

A: It can be used to assess early treatment response non-invasively and serially and cut animal costs in drug development research.

Q: What is your message to MISI?

A: I am happy to note that India has been an early entrant in the field of Molecular Imaging with leaders such as Dr. Swati Piramal and Dr. N. R. Jagannathan. With the momentum from these I wish MISI carries on with the same vigor.

Q: Your thoughts about collaborative research in the future?

A: I am open to collaborations which are synergistic.

Q: What is your advice to young researchers in this field?

A: Molecular imaging is an exciting area of research and there are plenty of opportunities. Ph. D students should actively follow literature and see what avenues they can identify in probe development, image processing, artificial intelligence for feature recognition.

Product Review

Each quarter, we will focus on an imaging product that will familiarize the readers with latest advances in the imaging field.

MULTI-PHOTON LASER SCANNING MICROSCOPE - TECHNOLOGY TO INVESTIGATE THE DEEPER COMPLEXITY OF THE THICK SPECIMENS

The theoretical concept of the multi-photon excitation was proposed by Maria Göppert-Mayer in 1931, and later this was achieved experimentally in 1961 after the invention of the laser. Two-photon microscopy was developed in 1990 by Denk, Strickler, and Webb. Two-photon excitation occurs as a result of the simultaneous absorption of two photons to excite a molecule from the ground to excited state. Two photons can interact simultaneously with a molecule adding their energies to produce an excitation equal to the sum of their distinct energies, that is, 2 red photons are equal to 1 blue photon because two photons arriving at the same time are required for excitation (Fig 1). The emission depends on the square of the intensity, rather than being linearly proportional. In vivo biology adapted this technique to understand the

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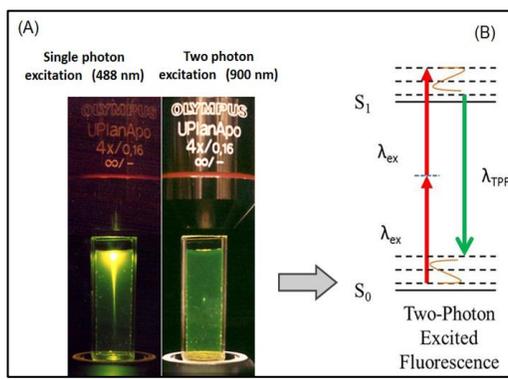


Fig 1: Principle of the Two-photon absorption process (A)

Comparative one and two-photon process show the excitation volume for both excitations¹. (B) Jablonski diagram indicating the absorption of two photons (red arrow) to excite the fluorescent molecule to an excited state (S₁) from (S₀) and the visible fluorescence emitted during relaxation (green arrow)

bimolecular system comprehensively. These techniques have significant advantages over the one-photon process.

The Olympus FVMPE-RS - A multiphoton laser scanning microscope is one of the most distinctive and powerful systems in the world. This system is dedicated only to the nonlinear excitation process of 2-photon excitation of endogenous fluorophores, which can be used to acquire horizontal optical sectioning of intact biological tissue samples. This system (Fig2) is designed for deep imaging in biological specimens to reveal how cells function and interact within living tissue. This microscope employs advanced technology and optical design to enhance sensitivity and resolution during deep imaging.

This system is designed for Depth-Brightness Compensation with thick specimens. It is integrated with Bright Z depth-brightness compensation, detector sensitivity, and laser power is continually

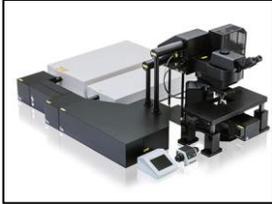


Fig 2: Olympus FVMPE-RS multiphoton laser scanning microscope

adjusted to maintain consistent brightness. This function complements the dynamic TruResolution objectives that also automatically adjust spherical aberration compensation with depth. This option reveals the structural morphology of submicron features such as dendritic spine

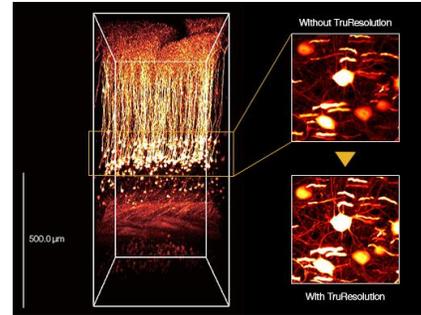


Fig 3: 3D reconstructed image of an in vivo mouse brain: Image captures using FVMPE-RS multiphoton microscope shows High-Resolution Deep Multiphoton Image. (Thy1-YFP-H mouse, sensory cortex) acquired using a TruResolution objective with an auto adjustment function (left) and maximum projection images acquired at an approximately 600 μm depth. Images acquired without (top right) and with (bottom right) the auto adjustment function. Images were acquired at the RIKEN BSI-Olympus Collaboration Center, courtesy of Dr. Hiromu Monai, Dr. Hajime Hirase, and Dr. Atsushi Miyawaki. (adapted from <https://www.olympus-lifescience.com/en/laser-scanning/fvmpe-rs/>)

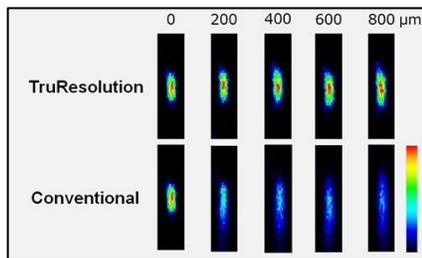


Fig 4: Fluorescent microbeads (diameter = 200 nm) in a gel with optical characteristics similar to live mouse brain (refractive index: 1.36, light scattering coefficient: 43 cm⁻¹) excited at 960 nm with constant laser power used for all images. (upper row) Microbead XZ images acquired at different depths using TruResolution automatic spherical aberration compensation. (lower row) Microbead XZ images acquired at different depths using a fixed correction collar initially adjusted for optimal imaging at the surface of the gel. Image brightness scales are normalized at each depth. All the images were acquired with the FV30-AC25W objective. (adapted from <https://www.olympus-lifescience.com/en/resources/white-papers/truresolution/>)

heads and necks are more clearly captured with neuron cells (Fig 3).

Olympus coming up with advance objectives called as TruResolution objectives it is extensively designed for automatic spherical aberration compensation and designed for deep observation and dedicated only for Olympus FVMPE-RS multiphoton laser scanning microscope. TruResolution objectives are equipped with a computer-controlled correction collar system that can automatically adjust to compensate for spherical aberration during deep observation of thick samples. When imaging deep within a sample using a multiphoton microscope, spherical aberration reduces fluorescence intensity and resolution. With the TruResolution system, dedicated software drives a motorized correction collar using

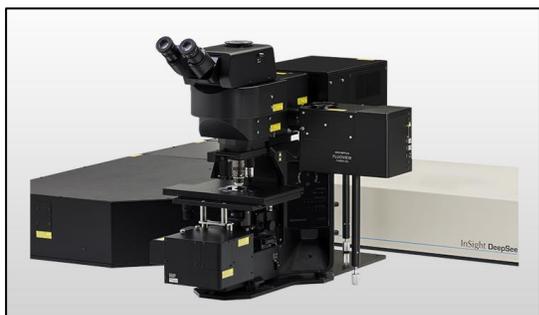
Olympus' unique algorithm, determining the optimum collar setting at each depth, quickly and accurately. For deep Z stack image acquisition,

In particular, the correction collar is automatically adjusted as you observe progressively deeper into the sample. As a result, the performance of TruResolution objectives can be maximized for all depths to acquire bright and high-resolution images. Figure 4 demonstrates the potent deep imaging capabilities of TruResolution objectives using fluorescent beads embedded in a gel with a refractive index and light scattering coefficient similar to those of a live mouse brain. The bottom row of images shows the gradual degradation of the focal spot as the observation region is advanced from the top of the sample, down to 800 μm deep, without adjusting the correction collar. Notable is the smearing of the images along the z-axis and decrease in peak intensity with depth. In contrast, automatic collar adjustment using the TruResolution system delivers a more consistent compact focal spot across the different depths. The top row of images clearly shows how TruResolution improves image brightness and resolution during deep imaging. The TruResolution system is also effective with cleared tissue samples. The Refractive index varies greatly between different tissue clearing techniques and may even vary between applications of the same technique. Olympus offers 3 Microscope Frame Options .

1. Upright Microscope System — For in vivo and in vitro multiphoton microscopy

This Upright Frame is completely dedicated to multiphoton microscopy. Providing space for large samples, a high degree of motorization, and nosepiece focus control enables the stage and your sample to remain fixed and stable. It is possible for the Detection of LightPath Designed for More Efficient Fluorescence Capture, Adjustable Design for the Various Sample Height Ex: The big focus stroke accommodates a wide range of specimens, from slices to mice and other small animals. It accommodates Comfortable Simultaneous Observation and Changes to Observation Conditions. The new double-deck design motorized fluorescence illuminator suppresses vibration to a minimum during mirror unit exchange. Observation conditions (i.e. multiphoton observation, fluorescence observation) can also be switched with minimal effort, even during simultaneous patch-clamp experiments. This system is available for SHG and THG Observation. The optionally transmitted fluorescence light detector expands your system's capabilities in multiphoton imaging. The dedicated high NA condenser detects transmitted fluorescence as well as transmitted second- and third-harmonic generation (SHG and THG) signals.

2. Gantry Microscope System — For in vivo observations that require more space



interfering light. The black microscope frame reduces undesired light reflections. This has the possibility for Three-dimensional Adjustment with a removable manual XYZ stage that enables height adjustments. Changing between the thin sample and whole animal imaging can be easily accomplished. It is coming with a large workspace

3. Inverted Microscope System — for in vitro observation of 3D cell (spheroid) and tissue cultures

The Inverted Microscope System is ideal for the time-lapse observation of thick cultivated cells such as tissue

The system with its ultra-stable arch-like structure, the new gantry microscope system offers a high degree of flexibility to suit different samples. This is ideal for in vivo observation requiring maximum space. This system is Intravital multiphoton microscopy with its ultra-stable arch-like structure, the new gantry microscope system offers a high degree of flexibility to suit different samples. This is ideal for in vivo observation requiring maximum space. It detection LightPath Designed for More Efficient Fluorescence Capture. The non-descanned detectors are very sensitive towards any



cultures, three-dimensional cultures, and cell cultures (spheroid), as well as intravital time-lapse observation of organs and tissues through a body window. This is an Inverted Microscope System is ideal for the time-lapse observation of thick cultivated cells such as tissue cultures, as well as intravital time-lapse observation of organs and tissues through a body window. This system is Ideal for 3D cultures and multicellular clusters (spheroids) This is an inverted frame ideally supports observations of 3D cultures and multicellular clusters (spheroids), which were difficult to manipulate with upright frames. It is improved for Non-descanned Detection. The optical performance of the IX83 fully automated high-end research microscope was optimized to efficiently collect scattered fluorescence light. Non-descanned detection performance is improved as compared to conventional inverted multiphoton microscope systems.



Conclusion

This most powerful Olympus FVMPE-RS multiphoton laser scanning microscope has distinct features

1. Optimized for deep observation. Deep Focus Mode Elevates Light-Condensation Performance for Specimens with Heavy Scattering. The Depth-Brightness Compensation Keeps Brightness Consistent from the Surface to Deep Levels
2. Detection LightPath Redesigned for More Efficient Fluorescence Capture. This setup is highly dedicated to a two-photon microscope.

3. The Deep Observation of In Vivo and Fixed Transparent Specimens Through Dedicated Multi Photon Objectives with a Maximum Depth of 8 mm. It is the maximum depth penetrable microscope in the market.

4. Specially designed Silicone Immersion Objectives for Live Imaging

5. This system contains high precision laser beam control up to 1300nm for flexible dual -Line Multiphoton imaging. InSight DS Supports Simultaneous Two Laser Line Excitation and Extended NIR Multi-Photon Imaging. It can auto Correct for Laser Beam Misalignment and Pixel Shift with Quadralign 4 Axis Auto Alignment

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3. Olympus Multi Photon Laser Scanning Microscope FVMPE-RS Catlog

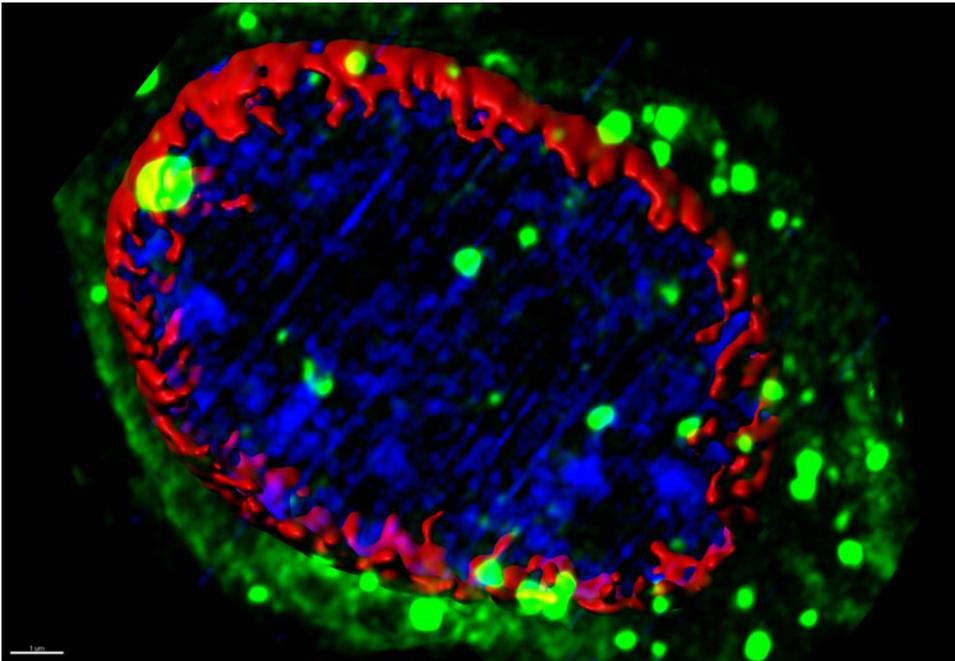


IMAGE OF THE QUARTER

Nuclear translocation of viral protein X (Vpx) of HIV-2/SIV: The illustrative image indicates that Vpx puncta localized at the nuclear periphery and progressively translocated into the nucleus. The viral protein X (Vpx) of HIV-2/SIV is the most important determining factor for the nuclear translocation of viral preintegration complex (PIC) in primary non-dividing target cells, which is essential for the formation of viral infection. We use super resolution-structured illumination microscopy (SR-SIM) to acquire the image in 3D and projected through Imaris volumetric image analysis. The inset shows the subcellular distribution pattern of oligomeric Vpx at the nuclear periphery in HeLa cells. Vpx (green) docked at the nuclear membrane is colocalized (yellow) with human Nup153 (red). The image shows that Vpx interacts with human Nup153 at the nuclear envelope and disrupts the nuclear envelope to enter into the nucleus (blue).

Every quarter, an outstanding image taken by our readers will be published. This quarterly, an image of a viral protein taken by Dr. J. Sebastian Raja during his post-doctoral stint at IIT, Madras is presented. I request readers to submit their images for this section through an email to: contactmisi.india@gmail.com

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OPINION

AI IN INFECTIOUS DISEASE: PROMISE OR HYPE?

Dr. Deepak Behera

President & CEO, Medical Imaging Consultancy, San Francisco, USA

What is AI?

For known history, mankind has used some sort of data analysis. Simple mathematical tools are generally sufficient for smaller datasets. More complicated statistical analysis may be required for larger datasets. When data is enormous with multiple variables and unknown associations and complexities, the traditional mathematical ways of deriving an inference fall short. How do we manage such data? How do we draw conclusions? How do we make sense of it all?

Artificial Intelligence (AI) takes computation to the next level by introducing cognitive aspects to big data analysis and unraveling the unknown and unanticipated.

Why is that important?

AI makes it possible to identify small signals from noise - thereby increasing our range of detection - and allows us to take preventative actions before everything explodes into a catastrophe! Perhaps similar to the change in our range of visibility when a fading headlamp in our vehicle is replaced by a super-bright halogen one. Translated to health care, this

means identifying a signature early and predict the rest of the course of a disease or an epidemic

Traditional computing algorithms are hard-coded. They produce robust results, but with known variables and data, and are unable to respond to unforeseen situations. Unlike physics and mathematics, the field of infectious diseases suffers from having multiple unpredictable factors that affect infection and transmission. When we attempt to apply a traditional computing solution to an infectious diseases problem, often as our understanding of disease evolves, new variables that weren't in the original algorithm surface and throw the traditional computational method off-course.

AI brings computing closer to emulating human cognitive functions by allowing machines to automatically and ceaselessly incorporate and contextualize new information. They observe, learn, understand, and respond to new data just as you and I would!



Deepak is a nuclear medicine physician-scientist turned executive, with roles of increasing responsibility in clinical development and medical affairs across clinical, academic, and pharma/biotech sectors. Currently, as the President and CEO of Medical Imaging Consultancy based in San Francisco, he provides strategic & operational advice & consulting to multiple pharma/biotech/device companies in the nuclear medicine/radiopharmaceutical industry. He also serves as the Secretary and Executive Committee Member, Board of Directors of the Indo-American Society of Nuclear Medicine. He completed his MBBS from Berhampur University and received his MD Diplomate of National Board in Nuclear Medicine in 2005. He was a translational researcher at the Department of Radiology, Stanford University. His research focus is on PET imaging of CD8 receptors, primarily for immunoncologic applications. He can be reached at deepak.behera@medicalimagingconsultancy.com

What can AI do for us in infectious diseases?

So, can we bring AI to infectious diseases? What problems can AI solve?

Can AI improve diagnosis?

The ability of AI to learn and synthesize predictions by combining relationships between a myriad of seemingly unrelated data can improve the accuracy and speed of diagnosis of infectious diseases. And often without the need for lengthy complicated tests. Or coordination between multiple players - doctor, patient, lab nurse, lab technician, microbiologist, office staff, etc.

As an example, a direct application of AI in the clinic - simple parameters from vital signs such as respiration rate, heart rate, and facial temperature – has been successfully used to classify individuals at higher risk for influenza, for instance [Sun et al. 2015].

Google already recognizes our faces and knows which photos belong to us. What if pathogens in patient samples could be identified faster without much human intervention using similar techniques?

Can AI help understand epidemiology and transmission?

In addition to a single time point diagnosis, could we use longitudinal and temporal data to arrive at individual patient-level or broad population/community level inferences? Detecting weak signals may predict events earlier than we currently can and may enable proactive (as opposed to reactive) intervention. Such intervention could

be at an individual level (e.g., prophylactic therapy) or at a population-level (e.g., allocation of resources in population-based outbreaks).

Doesn't that sound similar to the 'early detection of cancer' buzzphrase? Catch them early when they are small, and you can cure them. Or at least reduce the spread and/or complications.

In infectious diseases, the input data can be quite varied and out of the realm of analysis by mere human intelligence. Think of considering all factors at an individual level such as age, genetics, nutrition, lifestyle, co-existing diseases, pre-existing immunity, and behavioral traits, then merging it with extrinsic factors such as underlying infections in the community, interactions between members of the community, the prevalence of preventive habits, availability of healthcare, public policies, environment, and weather, etc. How about adding cultural differences, festivals, seasonal variations, and having a pet at home to the mix? Humanly possible? Perhaps, but maybe not for a sufficient number of humans to cover all possible infections in all large and small communities of the world.

Can AI be the machine to achieve it all?

Can AI help in treating infectious diseases?

AI could help in the proper treatment selection for each patient. In the clinic, therapeutic regimens could be adapted or personalized based on

factors such as body temperature, infection burden, clinical presentation, complications, drug sensitivity spectrum, contraindications, and drug-drug interactions. Algorithms could identify non-infectious causes of systemic inflammation and thereby reduce antibiotic usage.

AI could help identify immune or therapeutic responses. It can interrogate features of antibody responses to vaccines, and even characteristics of antibodies themselves to predict outcomes. Non-interventional methods could monitor patient factors, such as adherence to a treatment regimen, that may affect therapeutic efficacy.

AI could be used even in the drug development stage. It is already used to analyze large chemistry datasets to spot likely therapeutic drugs based on chemical and structural properties. Thereby simplifying the lead identification process in new drug development many-fold.

Okay, so what's the catch?

The possibilities outlined above are only some thoughts and examples, and by no means exhaustive. Many of us feel AI has a lot of potential. However, almost every shiny new technology is a double-edged sword. By definition, AI has a 'mind of its own'. To that effect, several questions remain to be answered.

- How do we safely achieve integration of such complicated technology in health and disease?

- How do we harmonize AI across multiple institutions, countries, states, populations?
- Can data collected for AI be misused for political or financial gains?
- Will AI take away our jobs?
- How will we protect ourselves against artificial stupidity – mistakes that artificial intelligence makes?
- Will our existing biases be magnified?
Example: [https://www.prop](https://www.propublica.org/article/machine-bias-risk-assessments-in-criminal-sentencing)

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Your thoughts:

What do you think? Is AI the solution to take our battle against infectious diseases to the next level? Or are we digging our own graves?

There are no right or wrong answers. Please share your thoughts, feelings, fears, and hopes.

References

Sun, G., Matsui, T., Hakozaiki, Y., Abe, S., 2015. An infectious disease/fever screening radar system which stratifies

higher-risk patients within ten seconds using a neural network and the fuzzy grouping method. *J. Infect.* 70 (3), 230–236.

Shen, Y., Yuan, K., Chen, D., Colloc, J., Yang, M., Li, Y., Lei, K., 2018. An ontology-driven clinical decision support system (IDDAP) for infectious disease diagnosis and antibiotic prescription. *Artif. Intell. Med.* 86, 20–32.

Dear Readers

Hope you enjoyed reading the first edition of the MISI newsletter. We would love to have your feedback about the same. Please send in an email to contactmisi.india@gmail.com giving your feedback. I also look forward to your contributions to the newsletter in the form of articles, images. Of course, I do hope that you will also join the MISI family as members and I look forward to fruitful interactions and networking among the clinicians, academicians, young researchers, experts, industries in providing solutions to healthcare challenges. I would also like to add that MISI will work in close collaboration with WMIS and FASMI for knowledge networking.

Please do not forget to post your feedback @ https://docs.google.com/forms/d/e/1FAIpQLSfaNBHMrIhgImMgWQfp7ztvBFHa-gbD3MujQ3_8nS9bAuKVzw/viewform?vc=0&c=0&w=1

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