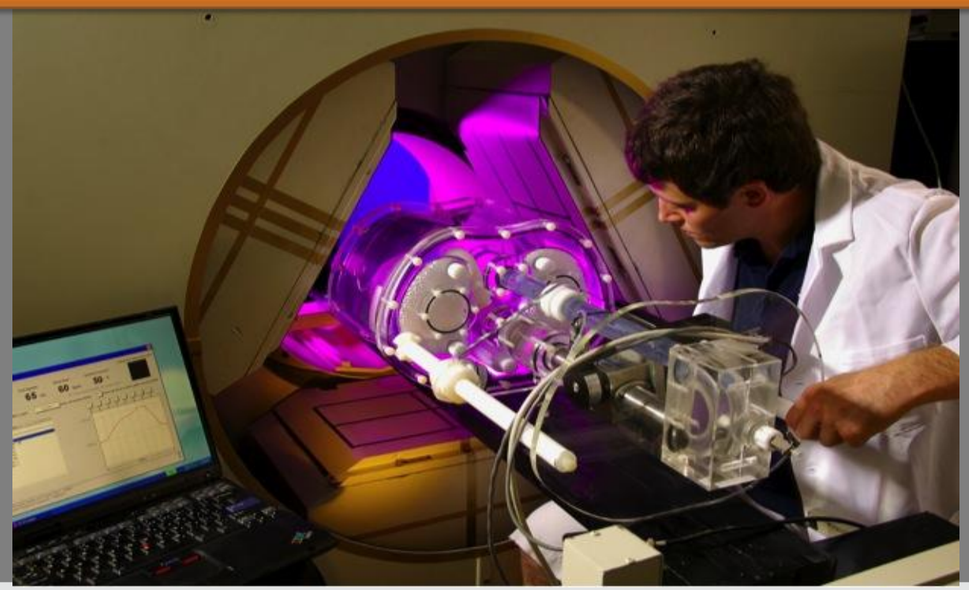
Molecular Imaging Lights the Way

For The Future of Medicine



We are now experiencing a transition away from the old method of treating cancer that included trying to detect tumors based on changes in normal physical anatomy, removing tumors as soon as possible, providing general anti-tumor medicines, and hoping the cancer was contained. A new way of treating this disease, based upon recent genomic advances in the understanding of the fundamental biology and chemistry of an individual's specific tumor, is upon us.

We know that the earlier a cancer tumor is detected, the better the chances of patient survival. Yet, in the midst of our genomic medicine revolution, cancers are still largely detected and diagnosed with the same procedures and technology used for a generation.

And that is where new molecular biomarkers (indicators of a specific biological state or condition) come in. Today thanks to the knowledge gained from genetic and molecular biology research, academic researchers and Medical Technology companies, including NuView Life Sciences, are developing the next generation of Molecular Imaging biomarkers for use in diagnosis of disease, assessment of treatment response and even targeted therapy. NuView has teamed up with two of the leading members in the field, both past Presidents of Society of Nuclear Medicine and Molecular Imaging, and are positioned at the leading edge of the Medical Imaging revolution. Mathew Thakur, PhD, Professor of Radiology and Director of The Laboratories of Radiopharmaceutical Research and Molecular Imaging at Thomas Jefferson University in Philadelphia and Peter Conti, MD, PhD, Professor of Radiology, Pharmacy, and Biomedical Engineering, , Director of the Molecular Imaging Center and PET Clinic at the University of Southern California are key drivers of NuView's Product Portfolio.

"We are clearly in the process of changing how a large number of different types of cancer are detected, diagnosed and ultimately treated. Molecular Imaging biomarkers are an essential part of this and the development of new imaging instrumentation, like the PET/MR, is clear evidence." said William G. Bradley, MD, PhD, NuView Life Sciences Medical Advisor, Professor and Chairman, Department of Radiology, UCSD Medical Center.

The Time is NOW

With the knowledge gained from a new understanding of genetics and molecular biology, coupled with advances in imaging technology and instrumentation, NuView is now able to identify transforming cancer cells through whole body or compartmental scans using highly specific imaging agents. Molecular Imaging helps us to achieve a kind of early-warning system at the cellular level — before any structural changes occur. With NuView's product portfolio, there is promise that a large number of cancers can be detected at their very earliest stages of disease and that therapy response can be measured directly and without delay. These products are able to detect key changes in biology and chemistry that accompany the development and proliferation of cancer.

"Each cancer is different and to manage it effectively, we need a better view and to gain a better understanding of the way the disease is developing. Then we can interrupt the complex network of proteins the disease uses to thrive", says Dr. Mathew Thakur, creator of the NLS–VPAC1 technology described below and a Scientific Advisor at NuView.

Complete Weather Map of the Body

NuView CEO, Paul Crowe, compares images produced from new imaging technology to that of a weather map you see on your local news. The radar images reveal the size and intensities of storms while the topological map of the United States displays an accurate depiction of the location and geographic features. When one image is overlaid with the other, people can see what areas are being affected by adverse weather so they can respond quickly.

In the same sense, by overlaying PET and CT or MR images physicians can more accurately locate, diagnose and treat disease at an earlier stage. CT and MR scans are the topological maps that can show broad areas of morphology while PET acts as the radar map that can show specific regions of biological or chemical changes within that morphology. For NuView, PET/CT or PET/MR imaging supplies both morphology and the biochemical changes occurring now that could eventually lead to the structural changes typical of advancing cancer over months or years. NuView is primed to take Medical Imaging to the next level.

Above: Imaging a patient on a PET/CT scanner

Demonstrated Efficacy

This is not theory – it actually works! NuView has been able to demonstrate efficacy and proof of principle for our products in animals and humans. The company has spent less than $5 million in the four years it has been active in the space.

NuView has sponsored laboratory and early clinical research with our academic partners at leading Universities. We then select only the best opportunities for advancement towards commercialization. This is where NuView is now with our NLS-VPAC1 and NLS-FMAU Molecular Imaging Biomarkers. We plan to initiate multi---center clinical trials of these products that will lead to their registration and commercialization in 2017.

Each one of these molecular imaging agents is something brand-new, never been done before and taking the technology a step further. Our Molecular Imaging agents will change the way cancer is detected, diagnosed and treated.

Personalized Medicine

There has been a great deal of talk over the last decade about genomics bringing about an era of "personalized medicine." NuView's biomarker technology represents another step along this progression.

If you have a chronic disease, it's a personal issue and it's different from one person to another. Using the weather analogy again, imaging biomarkers and PET can detect the "storms" on the map of morphology defined by the CT, and identify the spread of a disorder in your body in particular. But your map is different compared to the next person's. There's never a perfect square patch of cancer in your lung. It is personal, and it helps a physician set up a treatment plan just for you. And, with the biomarker already at the site of the potential tumor also comes the possibility of immediate treatment. The technology enables diagnostics to be paired with therapy at the molecular level.

It's a very personalized way to diagnose and treat a disorder. This is where the industry is going to head. No need to diagnose something after it's too late. "This is going to be a real game--changer, in our opinion", Crowe says.

Shining a light on breast cancer

Breast cancer awareness is being correctly ingrained in our public consciousness through highly successful campaigns such as Breast Cancer Awareness Month in October, which emphasizes the importance of annual mammograms for early detection. However, current technology cannot detect breast cancer at the earliest possible stages and it cannot determine whether a detected mass is benign or malignant. Today, diagnosis of cancer is still performed by extracting a sample of the mass through, painful and expensive biopsies procedures. There is a huge unmet medical need for early, accurate and non-invasive methods to detect breast cancer.

Today, a woman sees her doctor for an annual mammogram and receives the unsettling news that a "suspicious mass" has been found. What she wants next are immediate answers to questions. Yet, unfortunately, she will be subjected to a costly, painful and invasive biopsy, after which there will be waiting for lab results to be reported. And, 80 percent of the time, this entire process is unnecessary since the growth will turn out to be benign. Of the 1.6 million breast biopsies performed every year in the United States, about 1.3 million will result in a benign diagnosis.

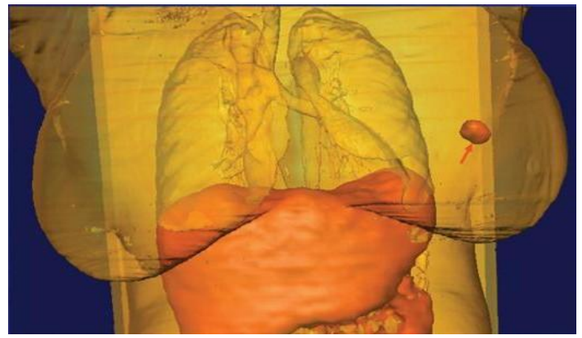
The inefficiency of breast cancer diagnosis is bad for patients and very costly to the health-care system in general. The ability to non-invasively determine the benign or malignant status of suspected breast cancer masses found by mammography will allocate invasive biopsy procedures, including surgery, only to patients that need them. NuView's NLS-VPAC1 will severely minimize the number of unnecessary, invasive biopsies conducted on cancer-free patients, spare them from physical and psychological trauma, and save billions of dollars each year in U.S. healthcare dollars.

Although great strides have been made in imaging breast cancer using MR, CT and ultrasound, they all suffer from serious limitations that prevent their utility in providing a definitive diagnosis.

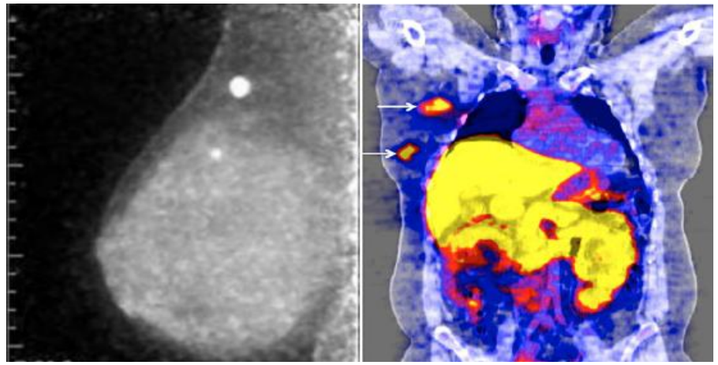
The glucose based biomarker (FDG) has also been investigated, but this agent is not cancer-specific and not sensitive enough for practical utility in diagnosing breast cancer. NuView's NLS-VPAC1 imaging agent is cancer specific and has shown great sensitivity women diagnosed with breast cancer.

How It Works

Our imaging agent attaches to the surface of cells that contain large amounts of a biomarker called VPAC1. These cells are cancerous as the surrounding normal tissue does not contain large amounts VPAC1 biomarker protein. Once attached to the cells, our imaging agent begins the second phase of its job. Our imaging agent has a passenger attached, Copper-64, a form of copper that is weakly radioactive, and as it decays, emits energy from the tumor to which it is bound. This energy is detected by a specialized camera, or what is commonly called a PET scanner. There are over 4,000 PET scanners in the United States being used in hospitals right now. This information transmitted into the PET scan is then transformed into a 3-dimensional image of the body and show the exact size and location of only malignant tumors, not benign masses. NLS-VPAC1 represents a huge leap over existing technologies by specifically visualizing cancer cells at the molecular level at early stages of disease.



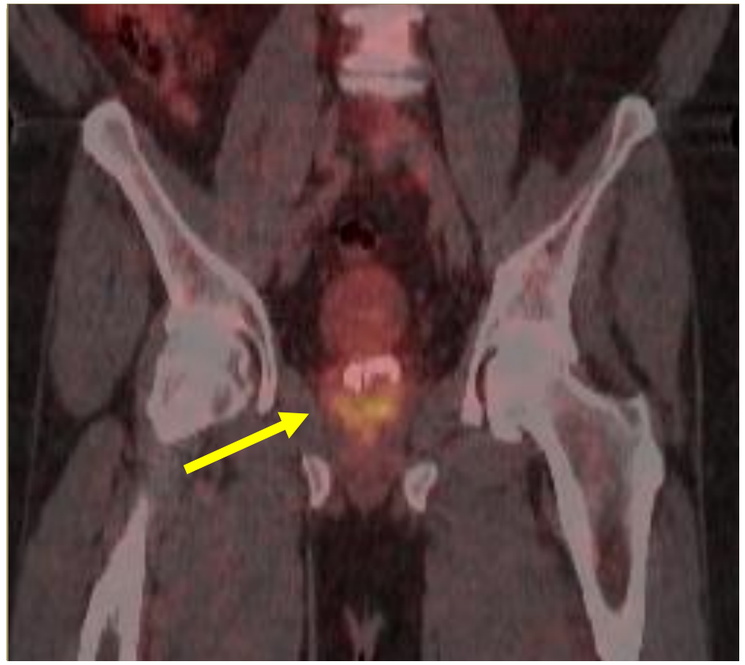
Above: PET Image of patient with malignant lesion of the left breast. Imaged with the NLS-VPAC1 molecular imaging biomarker



Above Left: PEM image of patient with malignant lesion in right upper right breast using NLS-VPAC1 biomarker.

Above Right: Whole Body PET image showing small malignant tumor in right breast and involved pair of lymph nodes in the axilla.

NuView is Getting Results
In a clinical study recently published in the Journal of Nuclear Medicine, a research team, led by Mathew Thakur, used FDG and the NLS-VPAC1 agent he developed with NuView's support, to image breast cancer in women newly identified with the disease by biopsy. The study was a tremendous success and identified all (100%) of the 20 lesions imaged. NLS-VPAC1 imaged all types of breast cancer and even identified all (100%) of the 4 cancerous sentinel lymph nodes. In a preclinical experiment, also published in the Journal of Nuclear Medicine, NuView's agent detected all eight malignant breast tumors in mice and did not detect the benign ones. FDG only detected four of the malignant tumors and imaged both benign lesions. The researchers said that current imaging techniques miss up to 30% of breast cancers and cannot distinguish between malignant and benign tumors.



Above: PET/CT image of a prostate cancer in a patient using VPAC1

Visualizing prostate cancer will redefine patient care

The detection and diagnosis of prostate cancer in men is fraught with many of the same problems as breast cancer. To start, both have unreliable screening methods – for prostate cancer, this consists of a PSA test and possibly a digital rectal examination. Like breast cancer, the next step in the path towards a diagnosis is performing an invasive biopsy procedure to attempt to obtain a sample of the mass for diagnosis. There is a huge unmet medical need for early, accurate and non-invasive method(s) to detect prostate cancer.

There are also differences in the current diagnostic environments for breast and prostate cancer. For some men, prostate cancer can be very slow growing with 'active surveillance' of disease being preferable to potentially painful and toxic therapies and decrease a patients' quality of life. For other men, the tumor is aggressive and necessitates surgical intervention with drug therapy. Services Task Force (USPSTF), the American Urological Association (AUA), and many other organizations have recommended against PSA testing for detection of disease. PSA testing has lead to overdiagnosis and overtreatment of disease. This means more men are receiving invasive biopsies and treatment procedures unnecessarily due to inaccurate screening for disease and the inability to accurately and non-invasively monitor disease progression. The result of these potentially unnecessary procedures is increased pain and morbidity including incontinence, impotence and serious infection.

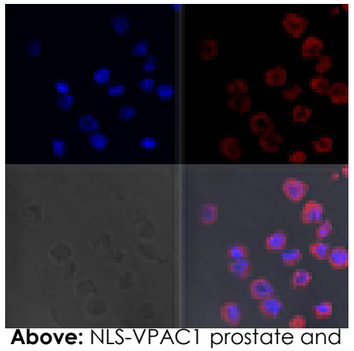
Another difference from the current breast cancer diagnostic landscape is the inaccuracy of prostate biopsy results. If a patient receives an elevated PSA test score and digital rectal exam, they are often referred for an invasive biopsy procedure for the diagnosing disease. Unfortunately, the procedure is a 'blind' procedure where the Urologist will usually take 10–12 samples of tumor with no knowledge of where or even if a tumor is present. Therefore, a negative test result does not rule out cancer, leading to increased anxiety in patients that can last for months and even years as the biopsy procedure is repeated.

NuView is developing two products, both based on Dr. Thakur's VPAC1 technology, to revolutionize the detection, diagnosis and treatment of prostate cancer.

NuView's first product in this space is a cancer-specific urine screen for the early and accurate detection of Prostate and Bladder cancer. Their aim is to replace the non-specific and inaccurate PSA tests that are leading to increased pain, morbidity and healthcare costs. By 2017, over $50 billion dollars a year will be spent worldwide on the detection and treatment of prostate cancer.

NuView's urine screen is designed to specifically detect prostate and Bladder cells that are released into the urinary tract. This test uses the same molecule as the breast cancer Imaging tool, but replaces the imaging signal used for PET cameras, with a different signal more appropriate for laboratory testing.

NuView and Dr. Thakur have already tested this screen on over 40 patients and healthy volunteers. The results again have been impressive, with 100% of the prostate and bladder cancer patients reading positive with 100% negative results in healthy volunteers and patients with other conditions, including a non-cancerous condition that leads to an enlarged prostate known as Benign Prostate Hyperplasia (BPH). BPH is currently difficult to distinguish from prostate cancer without an invasive biopsy.



Above: NLS-VPAC1 prostate and bladder cancer urine screen

The National Institutes of Health have awarded a $2.6 million grant to NuView and Dr. Thakur for a clinical trial currently enrolling patients to image prostate cancer

This screen alone would be a tremendous advance in patient care and reducing unnecessary healthcare spending. However, NuView is pushing this technology forward to specifically image prostate cancer tumors. Like in breast cancer, this would drastically reduce the number of invasive and costly biopsy procedures performed unnecessarily in cancer-free patients.

Today, over 1 million prostate biopsy procedures are completed each year in the U.S., with only 40% of these procedures positively identifying cancer. But equally important is what NLS–VPAC1 imaging can do for patients with prostate cancer. This product will give doctors and patients the ability to see the cancer. No longer will biopsies be performed blind. Urologists will know exactly where the cancer is for biopsy, reducing both the number of tumor samples needed and the rate of repeat biopsy due to uncertainty in diagnosis.

Also, seeing the tumor will be critical to retain confidence in active surveillance programs. Both the patient and the doctor will be able to see if or how fast a tumor is progressing and not rely on inaccurate PSA testing or additional biopsies. This will allow both the doctor and patience increased confidence in whether different treatment options will be necessary or potentially harmful.

NuView and Dr. Thakur have completed experiments in mice and published in the Journal of Nuclear Medicine that successfully show specific imaging of prostate cancer.

NuView and Dr. Thakur have received a $2.6 million grant from the National Institutes of Health to conduct a clinical study. The Medical Community is excited to learn the results of this study which started enrolling patients in the Fall of 2013.

Beyond Diagnosis: Visualizing patients' response to cancer therapy

Cancer is not a single disease but rather a constellation of different diseases – each tumor with different genetic components that behave in unique ways in unique individuals. No two tumors behave the same, and no two patients respond or are able to tolerate drugs or combinations of drugs the same. Currently, most cancer therapy responses are crudely measured by a reduction in tumor size, which will manifest long after a therapy has been administered to a patient. This leads to a delay in the

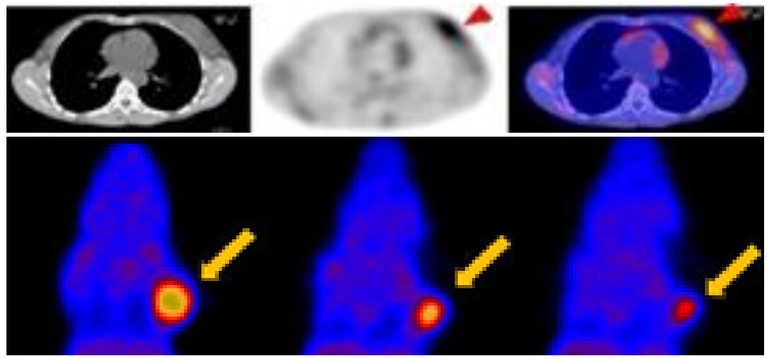
determination of the effectiveness of therapy, whether the dose level is necessary and sufficient, and whether a therapy change or termination is warranted. Despite the tremendous advances in personalized medicine and cancer therapy, there remains a large unmet medical need to accurately, quickly and directly assess whether an individual therapy is effective for an individual patient to provide the best treatment options and quality of care for the patient.

Currently, FDG is used in some situations to indirectly measure tumor metabolism of glucose. As previously mentioned, this agent does not specifically measure tumor cell growth and also images unrelated processes like inflammation, which can confuse or hide necessary information. FDG images can also change depending upon what type of therapy is used, regardless of the effectiveness of therapy. The ability to directly visualize tumor cells proliferating is what doctors and patients need to make informed decisions about the course of therapy.

This is where new Medical Imaging technologies can step in, offering new weapons for the fight against cancer. Visualizing tumor response to therapy may also offer critical support in another battlefield: drug development.

Imaging a shorter path to drug approval

Some potentially effective therapies may not kill current tumors, but rather inhibit the proliferation of new cancer cells. Therefore, a reduction in tumor size does not accurately assess whether a particular therapy is effective and much time will be



Above Top: PET/CT imaging in a breast cancer patient using FMAU
Above Bottom: PET imaging with FMAU displays a tumor response to breast cancer therapy in a mouse

wasted to determine that a tumor is NOT growing. This is critically important to Pharmaceutical companies in early stage clinical development. This product can display essential data to show quickly the drug is working, even if it does not rapidly reduce the size of a tumor. This will provide confidence to proceed to long and costly registrational trials that will determine the drug's effectiveness on the overall survival of the patient.

NuView is creating a courtside seat for the battle against cancer

NuView has licensed and is developing a molecular imaging biomarker from Peter S. Conti, MD, PhD, at the University of Southern California, to revolutionize the assessment of cancer treatments.

NuView's product hopes to provide the answer to a fundamental question in cancer management: Is the therapy working? NuView's imaging agent can *rapidly* provide information on whether the cancer cells are still proliferating after the administration of a particular therapy or if they have stopped. Another way of saying this is, if the therapy at the current dose level is working or if it is not. This product provides rapid flexibility for adjustments in dose level or switching therapies to provide the essential time needed for optimal treatment of the disease.

NuView and Dr. Conti have already shown their agent provides high quality images of proliferating tumors in the brain, bone, lung and breast, among others in a clinical trial. In the laboratory, Dr. Conti has produced exciting data to show dramatic visual changes in mouse lung tumors 2 days after treatment. Early next year, Dr. Conti will be starting a clinical trial to image the tumor response of patients undergoing treatment for breast cancer.

More Efficient, Less Costly

You may be asking yourself right now "How can an already financially stressed healthcare system accommodate these new technologies for widespread use?" The answer is an easy one These new medical imaging agents will save healthcare payors money. A lot of money.

The infrastructure is already in place for success. Large networks of Imaging Centers are currently in high volume hospitals. There are even large number of highly sophisticated mobile imaging centers in place. These mobile units allow access to high quality medical imaging in areas outside the care radius of a major medical center. The infrastructure is here, and better imaging agents are coming soon that will dramatically improve patient care while reducing costs.

Take NuView's Breast and Prostate Imaging Diagnostic, as an example. Currently, over 80% of women with an abnormal mammogram receive a benign diagnosis after biopsy. Replacing a painful, invasive and costly biopsy procedure with a non-invasive, disease specific and cheaper alternative is better for the patient and will save healthcare payors in the U.S. billions of dollars per year. Accurate diagnosis and visual monitoring of disease progression will reducing the overtreatment of prostate cancer. NuView's imaging agent will reduce the direct costs associated with unnecessary surgical and therapeutic interventions, as well as the indirect costs associated with treatment–related increases in patient morbidity.

Escalating cancer drug prices is a large concern in the healthcare industry, with some therapies costing over $35, 000 per month. The new and next generation of personalized therapies are highly effective, but only to a subset of the patients being administered the drug. NuView's agent for the visualization of tumor response to therapy has the potential to monitor in 'real-time' the effectiveness of a specific therapy on a specific individual. This new technology will be of great benefit to physician, patient and healthcare payors by decreasing time spent on costly or toxic therapies that are ineffective.

Diagnostic Biomarkers Lighting the Way to a Bright Future for Medicine

The genomic revolution has brought forth exciting new ways to detect, diagnose and monitor disease. From the laboratory to the molecular imaging department. This new approach of detecting visualizing of disease will provide higher quality, more efficient and cost effective patient care, genomic imaging biomarkers light the way.