

# Yale CANCER CENTER answers

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## **Clinical Applications of Research**

### **Guest Expert: Demetrios Braddock, MD, PhD**

*Associate Professor of Pathology, Yale School of  
Medicine*

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*Welcome to Yale Cancer Center Answers with your hosts doctors Anees Chagpar, Susan Higgins and Steven Gore. Dr. Chagpar is Associate Professor of Surgical Oncology and Director of the Breast Center at Smilow Cancer Hospital. Dr. Higgins is Professor of Therapeutic Radiology and of Obstetrics, Gynecology and Reproductive Sciences and Dr. Gore is Director of Hematological Malignancies at Smilow and an expert in Myelodysplastic Syndromes. Yale Cancer Center Answers features weekly conversations about the research, diagnosis and treatment of cancer and if you would like to join in, you can e-mail your questions and comments to [canceranswers@yale.edu](mailto:canceranswers@yale.edu) or you can leave a voicemail message at 888-234-4YCC. This week it is a conversation with Dr. Demetrios Braddock. Dr. Braddock is an Associate Professor of Pathology at Yale School of Medicine and here is Dr. Anees Chagpar.*

Chagpar Demetrios, tell me a little bit more about who you are, your background and what you do in terms of your research?

Braddock Basically I am a biochemist and a physician. I trained in biochemistry at the University of Chicago where I went to medical school and then I followed that with training at the National Institute of Health where I trained in chemical physics; the structure of molecules and their shapes and anatomic pathology. Currently at Yale what I do is I diagnose blood cancers as a hematopathologist and my research involves a family of enzymes that are kind of understudied and not really understood and they catalyze a very interesting biochemical reaction which is why I was initially interested in them. The reaction catalyzes the most unfavorable biologic reaction known to man, and this reaction, without the enzyme present, happens once every one trillion years, so that reaction will happen once in a trillion years unless the enzyme is present, so depending on your view of the age of the universe, it has never happened before without the enzymes, so we were very interested to understand what these enzymes did in the body physiologically, what their importance was because they catalyze such an unusual reaction and that has led me into the current direction of our research.

Chagpar I guess the first question is, how do you come across an enzyme that catalyzes a reaction that may never have occurred and how do you get interested in this particular enzyme if the reaction has not occurred yet and how do we know that it is important?

Braddock I should state that the reaction occurs all the time in the body because the enzyme is there, so the enzyme takes the reaction that would absolutely never occur without it being present and it happens several times a second, so it makes it very favorable and it does that by reducing the free energy of the thermodynamics of the reaction mechanism which is something we study as biochemists and organic chemists have been really interested in these reactions for years, probably 50 years, and it has been sort of the fascination of research in the chemistry field, but I think it has really been lost in the biologic field, the importance of these enzymes and so that kind of motivated my interest in them because basically, they are creating a very rare signal that never happens so when that signal happens, it is telling the body something really important, pay attention, this is an important event and so the body responds

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to that in big ways and in the case of one of the enzymes, it causes blood vessels to form and tumors to metastasize and in the case of another enzyme, it causes bones to form and calcium to build up or to disappear in your body.

Chagpar So big important reactions.

Braddock Yeah, these are key physiologic regulators of homeostasis in the body, so this is my theory, that these enzymes are key signaling events that govern whole organismal physiology and that is why we started looking at them.

Chagpar And so you started looking at them but what does any of that have to do with cancer?

Braddock Well one of the enzymes, the first enzyme really to be fully worked up which is the second enzyme in the family, is named NPP2, this enzyme was originally discovered in melanoma cells because melanoma cells secrete it and it causes melanoma to move and metastasize and develop in the body and so when I was at the National Institute of Health, my chairman at the time, Lance Liotta, discovered this enzyme and he introduced me to this family through this enzyme and we at Yale when we got here we looked at this enzyme, we looked at inhibitors to it and we showed that small molecule inhibitors can prevent tumor metastasis if you inhibit the enzymes activity and so forth and that work has now evolved into drug companies basically developing very sophisticated inhibitors beyond what we were capable of developing and those inhibitors are currently working their way through the clinical trial process.

Chagpar That is very cool, so is it just this one enzyme or are there other enzymes in this family that do equally cool things and that have been equally well worked up?

Braddock NPP2 was the most described in the study because of its role in cancer and when that field was moving very rapidly and I was unable to really chemically keep up with it because I am not a chemist, I am a biochemist, I began to look at other family members and I looked at the less well studied family members and that lead us into our current research which is looking at the first family member, NPP1, and this enzyme catalyzes a different reaction, completely different and it generates inorganic chemicals in the body called pyrophosphate and we knew that pyrophosphate was important for bone formation but we really did not understand how important it was and that got us into an investigation of what the role of this enzyme may be in the body and we began to study diseases associated with the enzyme and we came across a very rare disease in which individuals are born with a mutation in the enzyme and these babies tragically develop calcifications in their vascular system and they will die at about six months of age because of low levels of pyrophosphate, so that became a very interesting point of research for us.

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Chagpar And so then what happened?

Braddock So then we began to really think about how we could take our understanding and knowledge of the enzyme and manipulate lethal disease and we came up with a strategy to deliver the enzyme as a drug which involves modifying the enzyme so that you can inject it into the body and we did an experiment where we took mice that have this mutation, the same exact mutation that the humans have, and these mice also get vascular calcifications and they die within 30 days of life and we treated the mice with what we call a biologic which is an enzyme replacement therapy and we found that all the mice that we treated dramatically recovered from the disease. The enzyme therapy prevented the disease, the vascular calcifications, and they appeared completely normal whereas the mice that were not treated all died within 50 days, so it was kind of a black and white dramatic biologic experiment and something you do not often encounter in science.

Chagpar And so has this now been translated to humans, have we tried this in children?

Braddock We just finished that experiment which we call the perfect concept experiment, last year, a year ago about this time is when we completed that and so now you go through an FDA approval process where you take this data and toxicology data and additional data that you acquire and you file a package with the Food and Drug Administration to get what is called an initial new drug application, so this is the current state of this therapy. We feel that this is a metabolic disease and metabolic diseases are predicted very well in animal models unlike some cancers where the cancer can be cured in the mice and not in humans in some cases and in the case of metabolic disease, the animal models are actually very accurate for the patient, so given that it is a lethal disease, there is no therapy, there is no good cure, it is a horrible tragic disease, we are hopeful that we can move this into a clinical trial within 2-3 years.

Chagpar Excellent, so how common is this in children?

Braddock It is actually very rare and it is what we would call an ultra-rare disease, so the incidence is one in 350,000, so one person in 350,000 may come up with this disease. Now there are kindred's of patients where every fourth child they have will have this disease, so if you happen to be an affected individual and you are married to another effected heterozygote, we call it, you may have several babies with this, so it is tragic for those families and they may have a series of children that are partially or fully affected with this problem. But what we are understanding about this disease is that these babies also get renal failure and they present, either are born with or quickly develop, renal failure as well as vascular calcification and those processes are related, they are interrelated and it has to do with phosphate balance and the ability of the kidney to excrete phosphate and so forth and so even though this rare disease is very rare in a very select group of patients, there is a huge group of patients with renal failure, one in 10 adults has renal failure and the patients in renal failure also develop vascular calcifications,

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identical histologically to the calcifications in this very rare disease. They have a histologic signature where it is a medial wall so the calcification occurs in the muscle layer of the artery and that is very unusual in vascular calcification, so we think that the pathophysiology or the root cause of the disease in this rare instance in babies with this mutation is also the same cause in patients suffering from renal disease and can also be treated with this biologic, so we are pursuing this very common cause, and 2 million patients a year could benefit from some form of therapy to reduce their vascular calcifications and kidney failure.

Chagpar So in the renal failure patients, do they also have a deficiency in this enzyme?

Braddock That is not known, but we know that the renal failure patients have a low level of pyrophosphate and pyrophosphate is what the enzyme makes and it is the only enzyme in the body that makes that chemical, so we know that the renal failure patients have low pyrophosphate. We know that it correlates directly with vascular calcifications and we know that when we give the enzyme we can raise the pyrophosphate in mice, and we believe we can raise it in humans as well, so we are about as sure as we can be without actually doing that experiment that we can intervene in the process of progressive vascular calcification in a large cohort of patients that have renal failure and so that is a current long-term goal of the research as well.

Chagpar As we talk about this, two things come to mind, the first is that it seems that for the metabolic disorder in babies you have come across the answer in mice, which if you developed this drug, this enzyme could benefit, albeit, a very small population of patients, one in 350,000, and so you start thinking about the cost of the research, the cost of drug delivery and how much that whole process takes in order to help such a small fraction of the population and whether that would then translate into an extremely expensive medication and whether there is value in that if there is no benefit in the renal failure patients or whether if we find that this is actually beneficial for renal failure patients who are fairly ubiquitous, this may actually be of greater value. We have to take a quick break for a medical minute, but I would like you to respond to that when we come back, so please stay tuned to learn more information about basic research with my guest, Dr. Demetrios Braddock.

*Medical  
Minute*

*This year over 200,000 Americans will be diagnosed with lung cancer. More than 85% of lung cancer diagnoses are related to smoking and quitting even after decades of use can significantly reduce your risk of developing lung cancer. Clinical trials are currently underway at federally designated comprehensive cancer centers, such as Yale Cancer Center and at Smilow Cancer Hospital at Yale-New Haven to test innovative new treatments for lung cancer. Advances are being made by utilizing targeted therapies and immunotherapies. The BATTLE-2 trial at Yale aims to learn if a drug or a combination of drugs based on personal biomarkers can help to control non-small cell lung cancer. This has been a*

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Chagpar Welcome back to Yale Cancer Center Answers. This is Dr. Anees Chagpar and I am joined tonight by my guest Dr. Demetrios Braddock. We are talking about his latest research and clinical applications. For those of you who were with us right before the break, we were talking about his fascination with an enzyme or a series of enzymes, and one in particular, that catalyzes a reaction that if not present results in infant's dying, but it is so rare, only one in 350,000 births are affected. Demetrios, before the break, the question that I left you with was, how is it feasible, walk us through the steps of basic research all the way to getting a drug to market which presumably takes many years not to mention thousands or millions of dollars. How does that all work in terms of a cost equation ultimately to patients when a disease is as you called it ultra-rare?

Braddock Taking the first bite of the question, whenever you think about drug development, you have to be very aware of the potential indications and this is actually something that when I started at Yale 10 years ago, and I have a long term interest in drug development, I did not fully appreciate, so as we talked about I was initially interested in an enzyme that was important for tumor metastases and through conversations with oncologists at Yale, Dr. Mario Sznol who is at Yale who specializes in melanoma who was very instrumental in shaping my thinking, I came to understand that it was almost impossible to take an anti-metastatic drug through a clinical trial process because of the cost associated with completing that trial. It was just too much money and companies just could not do it and instead the better indications to look for are very lethal conditions that are very severe and these conditions do not necessarily need to be common conditions, they can be ultra-rare but if you can get a patient population that has them and that suffers from these conditions and treat them effectively with that drug, that becomes a financially doable problem for a drug company or development company and once you get it to the patients and you show its efficacy in this rare disease, you can then move into these more common diseases for indications that you would have never been able to develop that drug for in that first place. For example, we were talking about this very rare disease of vascular calcifications in infants and some of the perhaps philosophical barriers to spending a lot of time and money to develop a drug for these patients that are very rare, now if you go on websites and there are blogs and websites of these children, it is heart breaking to see those children die slowly and it is a tragedy for those patients, so we clearly want to intervene in those diseases for those people and we are committed to doing that, but it has an additional benefit to the larger society as a whole because millions of people suffer from a form of vascular calcification associated with renal failure and we believe that these patients will also benefit from the identical therapy, so you can develop a strategy of drug development where you go into a clinical trial for a limited number of patients, maybe only 10 or a dozen patients because it is a lethal disease, because this disease is very severe and death comes very quickly to these unfortunate patients, you can

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get through that clinical trial in a defined period of time which is extremely important when you are trying to develop what is called proof of concept for that indication, so the expense required by investors, by the venture capital community, who is the community that will ultimately decide whether the drug is developed or not, the exposure is limited. They know that they can spend 15, 20, 30 million dollars to get it through 10 patients and know they will have an answer at that time, so that is risk that is doable to a venture community and that is a risk worth taking, especially when you have on the backend this very large condition that may benefit, but to go into the renal failure population, the clinical trial may be years and the cost associated with that clinical trial will be exponentially greater, so that would be a daunting initial indication for drug development for venture communities and for companies, so you have to keep in your head as a translational scientist where you really desire to move therapy forward. You have to keep in your head both the scientific aspects of what you are developing but also the business aspects of what you are developing, because effectively if it is going to be developed it has to be developed by business and these were aspects that I think clinicians such as yourself, Dr. Sznol and Dr. Kluger helped me understand when I was a young investigator here at Yale looking at melanoma.

Chagpar I want to tackle a few of the issues that you brought up. The first is, clearly when you see these kids dying anybody would want to intervene, anybody would want to develop a drug that could be very effective and certainly your preliminary data have shown that it is very effective, and so a couple of questions. The first is, given the rarity of the disease, how would you actually do the clinical trial even to get 10 patients, when it is 1 in 350,000, would that not take a national/international collaborative venture to even get that kind of a clinical trial off the ground?

Braddock Yes, the answer is yes, but fortunately a lot of these rare diseases have what we call advocacy networks that are associated with them, so these are networks that are developed usually by the parents of children who have died of these diseases and they are committed individuals and they develop what is called a registry where other effected parents sign off and they record the progress of the child, all of the medical records are taken, and they are accumulated so that one can access these registries and have a very clean idea of the natural history of the disease in humans and this is very important when one moves into the FDA to present this data to them to convince them to allow for dosing and how you design the clinical trial that can cut years off, so most of these rare diseases will have some form of efficacy network and it is very important to plug into that. The other essential resource we have in this country is the National Institutes of Health where I trained and there is a rare disease program there and there are physicians who specialize in this disease and this family of diseases and they have families and patients that they see that travel to Bethesda to be treated and so one can tap into that network when one develops a therapy for a rare disease and use those governmental resources that have been invested wisely by our government to speed the clinical trial and to accumulate these patients, so even though it is a national and international endeavor to accumulate the patients in diseases such as this that are lethal and very severe, it is not a daunting process; it is a doable process.

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- Chagpar Because presumably people travel to those small areas that have the expertise in those rare diseases.
- Braddock Exactly and that is why there is such an interest right now in the drug development community on rare diseases generally. It has been demonstrated that even for these very rare diseases of 1 in 100,000, 1 in 200 or 300,000, it is not insurmountable, it is very achievable if it is done correctly and wisely, it is very achievable to enroll that trial within a limited period of time.
- Chagpar What happens to people who do not have the resources to fly to Bethesda?
- Braddock I believe that the costs associated with all of the transportation and the care is covered by the government, so if there is a clinical trial ongoing at the NIH, they pay for the transport, they pay for all the medical care fully.
- Chagpar That certainly does help. The next question of course is, so you do this clinical trial and let us suppose that it works and we now have a drug that in clinical trials has been found to save these babies, when that drug goes to market with the very specific indication of such a rare disease, would not the cost of the drug for that indication given the fact that we now do not have the indication for the renal failure which could presumably help millions of patients, be astronomical?
- Braddock The cost of the drug is really set by the industry and the idea is to recover the cost of drug development, so for these rare diseases where not much drug is going to be shipped, the cost is quite high, and this has been in the news a lot recently with some strategy of some pharmaceutical companies buying old drugs that are essentially off patent and then rising the cost of the drug by 100 fold to make it profitable. This is not the situation when you are developing novel therapies that require a huge investment in time and money, but typically the cost of these drugs is quite high, however, once that drug gets into the system and is approved for use in humans, physicians can use it in what is called an off label use and use it for other indications and that off label use may lead to further more common uses of the drug and this will in turn drive the price of the drug down because as it is used more commonly the price comes down in accordance with the amount of drug shipped, essentially, so in this particular instance with GASI, you may develop a drug that at first is extremely expensive but life saving and then the price of that drug may plummet over time if it is found to have efficacy in common indications such as renal failure.
- Chagpar For our listeners who might not know what GASI is, can you elaborate?
- Braddock GASI is general arterialized calcification of infancy and we just call it GASI to shorten that very long diagnosis and it is what it sounds like, it is a disease that develops in babies where they develop vascular calcifications that harden their arteries and they develop renal failure and heart failure and eventually expire usually around 6 months of age.

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*Dr. Demetrios Braddock is Associate Professor of Pathology at Yale School of Medicine. We invite you to share your questions and comments, you can send them to [canceranswers@yale.edu](mailto:canceranswers@yale.edu) or you can leave a voicemail message at 888-234-4YCC and as an additional resource, archived programs are available in both audio and written form at [yalecancercenter.org](http://yalecancercenter.org). I am Bruce Barber hoping you will join us again next Sunday evening at 6:00 for another edition of Yale Cancer Center Answers here on WNPR, Connecticut's Public Media Source for news and ideas.*