Virulence profile: Joshua D Nosanchuk

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What is Your Position at Your Institution?

I am fortunate to currently wear (or juggle!) several hats at Einstein. I am a Professor in the Department of Medicine in the Division of Infectious Diseases and in the Department of Microbiology and Immunology as well as an Assistant Dean for Students and an Attending Physician. Hence, I split my time between my laboratory, running our course for second year medical students in microbiology and infectious diseases (January-March), advising and mentoring students, and taking care of patients in our hospital.

Tell us About Your Early Days

My father was drafted into the US Army at the end of his Pathology Residency at the University of Michigan. So at the age of 3, I began to move a fair amount. I was in San Francisco, California, San Antonio, Texas, and Augsburg, Germany. After his service was complete, at which time I was 6 years old, we were next in Denver, Colorado, Rochester, NY and then, at age 13, Ithaca, NY. This meant I had to frequently make new friends, or at least I tried! What was “cool” in one place turned out not to be in the next. I learned over these moves that I had to be flexible, tolerant and very patient. The traveling with exposures to different cultures and attitudes also made me think of my “community” on a larger scale than many of my peers at the time, which has continued to impact my work and influences my enthusiastic and supportive approach to collaborations with investigators abroad.

Tell us About Your Education and Experiences at University. When did You Decide to Become a Scientist?

I have been attached to 2 institutions during my education and career. First Cornell and then Albert Einstein College of Medicine.

I was in high school in Ithaca, NY (“little Cornell”) and only went a short way up the hill to university, attending the College of Arts and Sciences at Cornell. Ithaca is an intellectually energizing small city that provided enormous opportunities for a curious and stubborn younger me; however, my research efforts as an undergraduate at Cornell were on deciphering the history of science rather than performing scientific studies. In the course of studying history and learning about the incredible impact that science has had on improving human health (although I focused on serendipitous findings, such as the identification of cortisone and penicillin), I discovered that I really wanted to be an academic physician rather than a Professor of History. I continued at Cornell for medical school, although the medical campus is in New York City. Along with learning a tremendous amount about patient care, I had opportunities to do both basic and translational research. One early experience was very important for teaching me about the experimental method and being critical with results. My roommate Thomas Ullman (now the Senior Associate Dean for Clinical Affairs at Mount Sinai and an expert in Inflammatory Bowel Diseases) and I worked on isolating RNA from wounded rabbit tendons following a “new” protocol published by a researcher at the University of Chicago. Despite all

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Submitted: 05/8/2015
Revised: 05/11/2015
Accepted: 05/12/2015
http://dx.doi.org/10.1080/21505594.2015.1058656
of our diligence, we were repeatedly flummoxed to end up with pure water instead of RNA. The laboratory director was increasingly frustrated with these two apparently incompetent medical students who were spending so much money on reagents and rabbits until he called the senior author of the methods paper we were following who sheepishly admitted that the protocol worked wonderfully on bone and muscle, but did not actually work on ligaments or tendons. Of course with PCR, these studies we were attempting would be simple today! However, I learned to meticulously follow protocols, troubleshoot reagent preparation, validate equipment, devour related literature, and, perhaps most importantly, be humble. I also learned the impact of incorporating patients into research in developing a study of muscle activity in patients with myositis. This work taught me the profound importance of respecting the patient participants, both for their time, patience, and willingness to occasionally undergo painful testing in order to facilitate our learning more about the pathobiology of their disease, with an often distant goal of the experimental work improving our ability to care for patients. In developing the study, I personally validated methods including having electrodes injected into my quadriceps that allowed us to measure muscle activity during various motions, and this further deepened my respect to these dedicated and willing study patients.

Where did You Perform Your Internship/Residency and What Field of Specialization did You Choose?

For residency training in Internal Medicine, I continued on at Cornell and the New York Hospital and Memorial Sloan Kettering Cancer Center. I engaged in several small clinical and laboratory studies, but the first project that resulted in a publication was a retrospective study on infectious complications after bone marrow or stem cell transplantation in patients with leukemia or lymphoma. Today, electronic medical records would dramatically simplify this task, but back in the mid-1990s finding charts was often a tedious process as charts could be in medical records or in doctor’s offices, clinics, administrative offices, etc. It could take several weeks to locate some charts! Anyway, I learned that writing a medical manuscript depended entirely on the patients with the diseases of interest and that the complex textual style that I had mastered as a history major was fundamentally not workable for a clinical journal, again teaching me the importance of humility. Moreover, the significance of identifying the right mentor was underscored as I was thoughtfully guided through this study by Kent Sepkowitz (now Deputy Physician-in-Chief for Quality and Safety at Memorial). Kent ripped my manuscript apart in a kind and constructive manner that I have tried to mimic in my editing to this day.

I finally departed Cornell for a research track fellowship in Infectious Diseases at Einstein and Montefiore. After a year of clinical Infectious Diseases training, I entered the laboratory of Arturo Casadevall, MD, PhD to explore the role of melanin in fungal pathogenesis.

Who Were Your Mentors?

I am indeed fortunate to have had truly skilled mentors. In terms of science, Arturo has been my primary mentor. Arturo selected a challenging project that rapidly immersed me in immunology, cellular biology, physics, and much more! I have worked with Cryptococcus neoformans (Figure 1) since stepping into the laboratory on my first day. Most importantly, he pointed me at the project and made me figure out how to accomplish complex experiments on my own. This independence allowed me to grow rapidly in the laboratory. Moreover, Arturo had me writing grants within 6 months of entering the laboratory, quickly setting the stage for the vast number of grant applications that I have since submitted. Arturo left Einstein this year to become the Chair of the W. Harry Feinstone Department of Molecular Microbiology and Immunology at Johns Hopkins Bloomberg School of Public Health, but we continue to work on fungal melanization, including our ongoing efforts to define the elusive structure of this pigment. I also need to acknowledge Liise-anne Pirofski, who is the Chief of Infectious Diseases at Einstein. Liise-anne, along with Arturo, has spearheaded an intense discussion on what a pathogen is, particularly focusing on the role of the host in facilitating the capacity of a specific microbe to cause disease in a specific individual. This critical approach to disease pathogenesis deeply impacted

Figure 1. This freeze-fracture scanning electron micrograph depicts the cell body of Cryptococcus neoformans (blue) surrounded by its polysaccharide capsule (purple).
my early thinking on infectious diseases, and also provided a wonderful platform for teaching. Liise-anne provided me with increasing opportunities to teach in microbiology and infectious diseases, such that I have directed basic science education in this area for several years. This also led to my work with the National Board of Medical Examiners (the group that creates and manages the tests required for medical licensure in the USA), at which I now have a leadership role. Throughout my experiences with them, both Arturo and Liise-anne have actively included me in research, teaching, and academic social activities, leading to opportunities that have significantly enhanced my career trajectory.

What Makes a Good Mentor?

I actually spend a lot of time thinking about this especially in my advisory Dean position, but also with how I can best assist the diverse group of students in my laboratory. I really like the idea of the “Yoda Factor”, which is a term coined by L. A. Daloz in the 1999 edition of Mentor: Guiding the journey of adult learners: “when mentors do their work well, they help us see not only the tasks before us but also the broader context that gives those tasks meaning. And like Yoda, they remind us of our destiny.” The best mentors do this and more, serving as a role model, introducing students to key contacts in their field, facilitating invitations to present in diverse environments, and critically and constructively evaluating their science, interpersonal behaviors, and communications skills in an ongoing manner. What is critically important and often overlooked by students is that mentorship requires the student to be fully engaged and proactive for true efficacy.

When and Where did You Start Your Own Lab?

As I noted, Arturo pushed me to write grants, which were absolutely necessary to allow me to continue in the laboratory. Without independent funding at Einstein, I would have returned purely to clinical work. In my fellowship, I successfully competed for a Medical Mycology Fellowship sponsored by the Infectious Diseases Society of America (IDSA) and Pfizer. With this 2 year award, I was able to put $7 each week into my bank account after paying for childcare, which was my only responsibility other than my research. My wife, a cardiologist, picked up the remainder of our expenses. However, this support from the IDSA was crucial. The effective progression of my fungal melanin research along with my strong mentorship support at Einstein allowed me to receive a KO8, a mentored physician-scientist award from the NIH. This also transitioned me from fellowship to an Instructor appointment at Einstein. However, my “lab” at this point remained within Arturo’s space, though I had my own equipment and a technician as well as undergraduate and graduate students. Also during this time, I received another award from the IDSA for immunology research on *Histoplasma capsulatum* and was a co-investigator on an RO1 with Arturo that derived from my KO8, research which we fortunately continue to be funded for through 2020. It was not until 2004, when I succeeded in competing for my independent RO1 on *H. capsulatum*, that I moved to my own space.

Were There Any People Who Influenced Your Decision?

My dad is the person who most influenced my career choice, albeit he did not specify medicine *per se*. On a chairlift ride at Jackson Hole in Wyoming during my Junior year in college, my dad told me that he was totally convinced that I would succeed as an academic whether I chose to be a history professor or a physician, but what he really wanted me to know was that I should never drive east in the morning or live more than ~20 minutes from work. Of course, I do drive east in the morning and have an hour drive into the Bronx, but I leave the house prior to the sunrise so at least I don’t have to deal with sun glare. Within Medicine, my dad’s career provided me with examples of how one could address clinical questions using basic and translational methodologies. Moreover, his dedication to continually improving the clinical laboratories he directed in order to provide optimal care for patients underscored early for me the critical fact that the end goal of our efforts as physician-scientists is to improve human health, which is a lesson I constantly pass forward to my students.

What do You Like Most About Your Work as a Physician?

I love thinking. Each patient is a new challenge, a different puzzle: what is making this person sick? I make sure that I not only decipher the disease process in the individual patient, but also how I can best connect with the patient to carefully communicate what I think are the key points of the patient’s illness to him/her, which can be challenging in the diverse Bronx community within which I work. Moreover, I thoroughly enjoy doing this in collaboration with medical students and residents, showing them my thought process and striving to help them become better caregivers while concomitantly underscoring the importance of the basic science foundations of medicine, meaning that the students need to know disease pathobiology, the function of the immune system during health and illness, the mechanisms of medications, etc.

How can one Successfully Combine Working in the Clinic with Head ing a Research Lab?

The best factor in this duality is that each informs the other. Taking care of diverse individuals with various medical diseases shows me directly how much we still don’t know, and this also informs me directly of what new knowledge or treatment approaches could improve our capacity to care for patients. Efforts in my laboratory are geared to generating these new insights on the diseases I research as directly of what new knowledge or treatment approaches could improve our capacity to care for patients. Efforts in my laboratory are geared to generating these new insights on the diseases I research as well as on developing innovative diagnostics and therapeutics. This synergy enhances my enthusiasm for what I do and makes me a better advocate for other physician-scientists.
However, the question is on successfully combining being a clinician and an investigator. You need to carefully carve out dedicated time for each role, while acknowledging that all of your responsibilities want your full focus all the time. When you are with a patient or are expected to be with a patient, your other obligations absolutely need to take a backseat. When you are attending in the hospital, you have a grant deadline, students are emailing for advice on experiments or their careers, etc., the most important key to success is to keep calm and be nice. My ears will get red as an indicator of my frustration, but taking one’s time to complete tasks in a prioritized fashion facilitates success much more readily than passing your pain onto others either through words or actions.

One of the other difficulties is that I don’t have time to read everything I want in Medicine or my areas of research. I have found, however, that I can largely keep abreast of my fields by reading whatever I can and supplementing this with the reading and learning that I do by reviewing lots of papers for diverse journals. Also, I use keyword searches in PubMed to routinely notify me of new publications in specific areas of interest.

How Many People Work in Your Lab?

This is a dynamic number, though it has been ~7 people for the past several years. Over the summer, it can swell up to 12 people with high school and university students, though I have really restricted this number the past 3 years since assuming my Dean position, as I am less often in lab to oversee these junior students.

What Areas or Topics Does Your Lab Currently Focus On?

There are two sections of my laboratory at present, one focusing on fungal pathogenesis and the other on wound healing. Fungal melanin is tightly associated with virulence in numerous species, though we primarily utilize C. neoformans as our model organism since we can closely control melanin formation in this species. We continue to delve into how melanin is formed and to define what the structure of this enigmatic polymer is. The second major area in fungal biology is our efforts to determine the effects of antibody on H. capsulatum. A third active area focuses on virulence factors of Candida parapsilosis on which I collaborate with Attila Gacsar, a Professor in Szeged, Hungary who is a former post-doctoral investigator from my laboratory. There is actually currently overlap of all of these programs as we are investigating the role of vesicle secretion by fungi in melanization and virulence as well as in responses to antibody. With collaborators, I am also currently studying Sporothrix species, Paracoccidioides species and dermatophytes.

I became interested in wound healing given that wound infections, especially in chronic wounds, are an extremely common and debilitating issue in our patient population as well as globally and that colleagues of mine at Einstein had novel compounds that could be used as antimicrobials that simultaneously enhanced wound healing. With Drs. Adam and Joel Friedman we have been exploring the utility of an innovative nanoparticle platform that delivers sustained levels of nitric oxide or other therapeutics. More recently, I have been collaborating with David Sharp, PhD in an exciting project in which we regulate microtubules within cells to enhance tissue regeneration.

Do You Have Partners That are Important for Your Research Projects?

I am a firm believer that you are always stronger as a team than you can be as an individual. This is especially important in the setting of financial pressures that we face with low successes with funding. I continue to work closely with Arturo on fungal melanin, but I also collaborate in this area with Beatriz Gomez, PhD in Medellin, Colombia and Sirida Young-chim in Chiang Mai, Thailand. My studies on targeting melanin therapeutically for infectious diseases and for melanoma has been achieved in collaboration with Kate Dadachova, PhD, a talented radiobiology Professor at Einstein. My former post doctoral student, Luis Martinez, PhD, MBA, a professor at New York Institute for Technology, and I have several joint studies, including on fungal biofilms, methamphetamine, and host response. As noted above, I collaborate very closely with Attila on Candida pathogenesis as well as with the Friedmans and David Sharp on wound healing.

Also, I have had a simply wonderful and rich history of collaboration with Brazilian scientists, supported both through an NIH Fogarty award as well as with grants from the Brazilian government. My collaborations with Brazilian scientists initiated in Arturo’s laboratory where Carlos Taborda, now a Professor in Sao Paolo, Brazil, came for a post-doctoral fellowship. Carlos and I have continued to work closely together and we have published 13 papers over the years. Though my first collaborator in Brazil was Rosely Zancopé-Oliveira from Rio de Janeiro, with whom I leveraged my knowledge of immunology and pathogenesis to work on serological diagnostics, and we have co-authored 14 papers. My first graduate student, Allan Guimaraes, came from Rosely’s laboratory, and Allan is now an independent investigator in Niteroi, which is a sister city to Rio. Allan and I continue to collaborate on projects pertaining to antibody and virulence factors, and we have 22 papers together. Since 2007, I have worked very closely with two other Professors from Rio, Marcio Rodrigues and Leonardo Nimrichter, and, between these scientists, I have co-authored 15 papers. For the past 3 years, I have spent ~1 month annually in Brazil working in the respective labs of these bright and very fun investigators as well as giving lectures and workshops, supported through a grant awarded by the government of Brazil. I have also hosted many visiting students from their labs, and Leonardo was previously funded through Fulbright to spend an extended period with me at Einstein. At the beginning of this year, I received an NIH supplement through a joint NIH-Brazilian program in collaboration with Arturo and Anamelia Bocca and her colleagues in Brasilia, Brazil for studying fungal vesicles. Hence, I think it is very clear how important collaborations are to me, both within Einstein and globally!
What are Your Main Goals for the Next Five Years?

In the laboratory, I really want to know why two of my monoclonal antibodies to the same epitope on the cell surface of H. capsulatum function in diametrically opposite manners, with one providing significant protection and the other enhancing disease. After several years of attempts to genetically manipulate these antibodies, I am now finally poised to figure this out. With my collaborators, I want to more fully understand the biology of fungal vesicles as well as determine the pathways for their synthesis and how they are regulated. I want to continue to leverage my laboratory to advance the ability of scientists in developing nations to achieve the goals of their research.

In my educational roles, I will continue to diligently work at Einstein, with national/international infectious diseases and microbiology associations, and with the National Board of Medical Examiners to assure that the basic sciences have a major, impactful role in medical education. It is science that drives medical advances and collaborations between physicians and investigators bring about remarkable opportunities for moving discoveries rapidly forward from innovative ideas initially tested at the bench to delivering these as rigorously tested therapeutics to patients.

Tell us About the Most Important Stages of Your Professional Career

Each stage is critical, but the most important stage is where you currently are as what you do now is what really matters for moving you ahead to the next phase of your career. If you don’t continue to publish, receive funding, actively participate in community service (ie. serve on institutional committees, sit on study sections, serve on editorial boards, review manuscripts, etc), teach and more, you will not advance. With that said, what you do as a junior investigator sets the stage for what follows. Having your mentors advocate for you can allow you to become known in your field, which will facilitate socialization at meetings, lead to invitations for lecturing at conferences or outside institutions, and have name recognition when your grant comes before a study section.

What was Your Most Significant Scientific Accomplishment?

This is a hard question. I think the achievement that has paid forward the most in my laboratory as well as in terms of a resource for others is the generation of melanin-binding reagents, both monoclonal antibodies and phage. These reagents allowed me to definitively demonstrate that melanization occurs in C. neoformans, as well as other fungi, during mammalian infection, supporting research into this virulence factor. Moreover, we have used these reagents as therapeutics for melanoma, completing a phase 1a/b clinical trial. Additional accomplishments that I am proud of include proving that antibodies are relevant in histoplasmosis, that modifying host cell co-stimulation can impact response to fungal infection, developing a system for gene disruption in C. parapsilosis, and identifying that extracellular vesicular secretion is a conserved phenomenon in ascomycetes and basidiomycetes.

What Advice Would You Have to Junior People Entering the Field?

Collaborate, be helpful to your scientific community, applaud colleagues’ and competitors’ successes, and work really, really hard to get your papers and grants out are key activities at every stage. Identify and work closely with the right mentor. However, the best advice I have is that you should figure out what you love to do and do it.

What do You Think You Would do if You Were Not an MD or a Scientist?

I would have become a history professor. Deciphering the activities of the past can be an intellectual adventure that I find not far different from working out the cause of a patient’s symptoms.

What do You do or Fun?

I love to travel, and fortunately so do my two boys and my wife. We leave the US at least twice a year as a family. I want my boys to know that the world is bigger than our small town, and that there are many ways to live. I want my boys to see what is “out there” for them to challenge themselves with in their future careers. Along with the traveling, I enjoy trying new foods, whether it is street food or that found in Michelin-starred locales. I also enjoy watching certain shows, such as Dr. Who with my younger son and Game of Thrones with my wife. I try to meet up with friends and colleagues as often as possible, especially if there is a nice bottle of wine involved.

About Joshua D Nosanchuk. Dr. Nosanchuk received his undergraduate degrees in History (1988) and Medicine (1992) from Cornell University. He further developed his education during an internship at New York Hospital-Cornell and Memorial Sloan-Kettering Cancer Center (1992 5), and fellowship at Albert Einstein College of Medicine (1995 8), where he later held various academic positions and currently is a professor at Departments of Medicine and Microbiology & Immunology as well as Assistant Dean for Student Affairs. Along with teaching and running his lab at Einstein, Dr. Nosanchuk has been an active physician in Internal Medicine and Infectious.
Diseases at Jacobi Medical Center (1998–2008) and Montefiore Medical Center in Bronx, NY (since 1998). His research focuses on pathogenic fungi, especially *Cryptococcus neoformans* and *Histoplasma capsulatum*. He has authored almost 200 scientific papers, nine book chapters and three patents. Dr. Nosanchuk is a recipient of numerous awards and honors, including Davidoff Award for Excellence in Teaching (2003), Wyeth Vaccine Young Investigator Research Award (2004), Henry L. Moses Award, First Prize in Basic Science (2005), Hirschl/Weill-Caulier Career Scientist Award (2009) and Samuel M. Rosen Outstanding Preclinical Teacher Award (2015).