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Sandia National Laboratories: Biosciences:

Interview questions for Dr Malin Young, Senior Manager of the Biological Science and Technology Group

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1. Firstly, could you offer an overview of the Biological Science and Technology group at Sandia?
   Sandia's Biological Science and Technology program works primarily in the areas of biodefense, emerging infectious disease, and cellulosic and algal biofuels. The basic and applied research and development activities in our group are multidisciplinary and cover a broad range of areas including cellular signaling, host-pathogen interactions, enzyme structure and function, lignocellulosic biomass deconstruction, synthetic biology, metagenomics and proteomics, advanced spectromicroscopy, microfluidics, and clinical diagnostics. Key sponsors of our research include the Department of Energy, the Department of Defense, the Department of Homeland Security, and the National Institutes of Health.

2. Can you explain your main mission and how this has evolved over time?
   Sandia is a National Security Laboratory, so our focus is on addressing important national security challenges. Our main mission is to reduce the national security risks posed by emerging, existing, or engineered biological threats and our Nation's reliance on fossil fuel. The set of challenges our group has addressed has evolved with changes in the national security environment – for instance, after the Amerithrax attacks in 2001, we became very engaged in supporting the efforts of the Department of Homeland Security to protect the Nation from biological attacks. As the promise of biologically-derived fuels grew, we began working on developing lignocellulosic biofuels as a founding partner in the Joint Bioenergy Institute (JBEI). In the wake of the SARS and H1N1 outbreaks, we recognized that naturally emerging biological threats pose a serious national security threat. In response, we expanded our biodefense program and now are working closely with Sandia's International Biological Threat Reduction (IBTR) program and collaborators around the world to develop global disease surveillance capabilities to quickly detect and characterize new pathogens as they emerge.

3. How does the Group contribute to the wider aims of the Sandia National Laboratories? Could you offer some examples?
   Sandia's core mission remains the safety, security, and reliability of our nation's nuclear stockpile. However over the past 10–15 years, our work in broader areas of national security— including homeland security, energy security, military preparedness, cyber security, and intelligence—has grown and diversified. Work in

these "broader national security" areas currently constitutes ~60% of the Lab's overall work.

An important element of Sandia's national-security mission is to provide solutions that help protect the security of our homeland and our military forces against the threats of biological weapons, acts of terrorism, and newly emergent pathogens. Since the mid-1990's, Sandia's contributions in biodefense have spanned a broad range of activities ranging from the design of defensive architectures and concepts of operations, to the development of biodetectors, diagnostic systems, and decontamination formulations, to the design and test of operational systems. A specific example: In 1997, DOE funded Sandia to begin development of new types of biodetectors based on microfluidics technologies. Sandia workers developed and tested both hand-held and fixed biodetection devices which were capable of rapidly detecting biotoxins, viruses, and bacteria. This work led to the creation of five startup companies, one of which, Eksigent, currently employs over 100 people. In the early 2000's, the NIH began funding work at Sandia for use of the underlying biological detection technology in rapid, portable, easy-to-use medical diagnostics. Sandia scientists are currently developing systems capable of detecting biotoxins and markers of rickettsial infection and radiological exposure.

Sandia's biofuels program focuses on the development of transportation fuels from cellulosic and algal biomass. Sandia is a core partner of the DOE Joint BioEnergy Institute (JBEI), led by LBNL with LLNL, SNL, UC-Berkeley, UC-Davis, and the Carnegie Institute. In JBEI, Sandians are leading R&D efforts to convert lignocellulose into fermentable sugars and develop new multi-dimensional analytical technologies to understand and manipulate the bioconversion process. Sandia's algal biofuels program includes projects ranging from the Sustainable Algal Biofuels Consortium (SABC) led by Arizona State University, a DOE OBP-funded Pond Crash Forensics Project to better monitor and manage algal raceways, and the Sapphire Energy Inc.-led Integrated Biorefinery Project.

4. What types of global challenges is the Group hoping to address in its research?
We work to address the global challenges posed by the emergence of new biological pathogens and the proliferation and use of traditional and engineered biothreats, and we foster greater energy independence through the development of alternative biofuels. To this end, we work within an international network of collaborators to conduct our research and to translate our results to operational settings. One area that we have recently begun to explore is the development of diagnostic systems that can operate in low resource settings. Such systems would make complicated assays that are currently run only in centralized laboratories by highly-trained

individuals available to smaller clinics which have minimal power, operational infrastructure, and trained personnel.

5. To what extent do the departments within the Group collaborate with other Sandia teams? How interdisciplinary is your research?

   Sandia is a highly interdisciplinary Laboratory that exists to solve very tough National Security R&D challenges. The Biological Science and Technology Group is no exception. Our capabilities include experimental competency in “omics” (genomics, proteomics, etc.) as well as world-class biotechnology capabilities (e.g., biomolecular imaging, computational biology, microfluidics, and bionanotechnology). Since we are so interdisciplinary, we have the ability to bring together combinations of seemingly disparate laboratory resources that result in a powerful engine for discovery science focused on these challenges.

   In addition we collaborate broadly with other groups within and external to Sandia as needed to augment our capabilities. Several specific examples of collaborations I’ve already mentioned are JBEI and our IBTR program, but we work extensively with other National Laboratories, federal entities such as the Centers for Disease Control and Prevention (CDC), and industrial and academic partners to achieve our goals.

6. A large proportion of the Group’s work is on biodefence and emerging infectious disease. Could you outline some of the research currently being conducted in this area?

   Our group is focused on quickly detecting, identifying, and characterizing accidental, natural, or deliberate outbreaks of biological agents and reducing the impact of those outbreaks. Our objective is to develop and apply integrative bioanalytical systems and approaches to quantitatively define and detect host and pathogen indicators of infection or exposure in complex clinical or environmental samples, and provide end-users with actionable information they can use to develop an effective response.

   To this end, we are applying Sandia’s traditional strengths in engineering and technology development to gain basic knowledge regarding the fundamental molecular processes of pathogenesis, including the dynamic interactions between microbial pathogens and their hosts, and to develop assays, novel materials, and platforms to detect and diagnose traditional and unknown pathogens.

   The basic and applied elements of our biodefense research program are tightly linked. By investigating host–pathogen interactions, we not only provide a deeper understanding of how diseases originate and develop, but we also identify new ways to detect, interdict, and mitigate emerging infectious diseases. So by exploring the biological principles underlying known and emerging infectious diseases, our researchers are accelerating the development of technologies to detect and diagnose biological weapons that threaten the security of our homeland and our troops.

A specific example of how we bring together our science and engineering capabilities to achieve a concrete objective is the Rapid Threat Organism Recognition (RapTOR) project. The RapTOR team consists of molecular biologists, engineers, and bioinformaticians all focused on a common goal: to develop a system for the rapid identification and characterization of unknown pathogens in clinical samples through suppressive molecular biology methods and second generation sequencing (SGS). Their collective efforts resulted in the development of an Automated Molecular Biology platform for automated SGS library preparation that won the Society for Lab Automation and Screening 2011 Innovation Award and a 2012 R&D 100 Award. They have also invented new molecular biology methods that increase the sequence hits to an unknown pathogen in a clinical sample by nearly 2 orders of magnitude. The RapTOR methods are currently being transitioned to the CDC for testing and evaluation, and its products are currently being applied to diverse applications ranging from algal pond health monitoring to battlefield forensics.

7. In what ways are the Group's cellulosic and algal biofuels projects contributing to the movement towards clean, green, and renewable sources of energy in the US and beyond?

The need to develop clean, green, and renewable sources of energy has become an international call to action. Sandia researchers are working to reduce U.S. dependency on foreign oil by focusing on transportation biofuels derived from both cellulosic and algal biomass. In a way that is analogous to our approach to biodefense, Sandia's biofuels scientists are conducting fundamental investigations and then using their findings to move the world closer to the day when fossil fuels will be largely replaced by biofuels. We take a systems view of biofuels development – we not only conduct research to enhance biofuels production, but we also examine the sustainability and environmental impact of biofuels production and use.

8. Can you summarise some of the Group's current biofuels research?

Our renewable fuels program is centered on 2 sources of feedstock biomass: lignocellulose and algae. Our core program in lignocellulosic biofuel development is JBEI, led by LBNL in partnership with LLNL, SNL, UC-Berkeley, UC-Davis, and the Carnegie Institute. Sandians are leading R&D efforts at JBEI to convert lignocellulose into fermentable sugars, and developing new multi-dimensional analytical technologies to understand and manipulate the bioconversion process. In algal biofuels development, we have funding from DOE for the Sustainable Algal Biofuels Consortium (SABC) led by Arizona State University in partnership with Sandia and

NREL, the Pond Crash Forensics Project which leverages our RapTOR technology, and the Sapphire Energy Inc. Integrated Biorefinery Project.

9. What are your personal research interests and what led you to this position at Sandia?
   My personal research interests have been most recently focused on the development of a rapid, moderate-resolution structure determination technique called MS3D (Mass Spectrometry in 3 Dimensions). MS3D derives inter-atomic distance constraints for proteins, nucleic acids, or their complexes, from chemical cross-linking and mass spectrometry experiments. These distance constraints are used in conjunction with predictive methods to construct moderate resolution structural models for a given macromolecular target.

   As a computational biologist, I have found close collaborations with experimentalists to be tremendously rewarding, which has fueled my appreciation for multidisciplinary team science. When I interviewed at Sandia, I found a place that lives and breathes team science in the service of solving important national problems. Sandia was just beginning to build its biology program at that point, and I saw an exciting opportunity to be part of developing a program from the ground up that was inherently multidisciplinary and National service-oriented. How could I resist?

10. In your opinion, what has been the greatest achievement of the Group to date?
    This is a difficult question. The group has performed exceptional research and development over the years and it's hard to pick a favourite. So I won't. Instead I will give you a few highlights. One is founding the Joint Bioenergy Institute with LBNL and our other partners. JBEI is one of only three Bioenergy Research Centers in the Nation, and the work it carries out is extremely important to increasing our nation's energy independence. Another highlight is the RapTOR team's development and application of molecular suppression methods, automated library prep platforms, and SGS to a broad suite of national security challenges. A third highlight that comes to mind is the NIH New Innovator Award won by one of our researchers, Jeri Timlin, for her project "Multiplexed measurements of protein dynamics and interactions at extreme resolutions." Jeri was one of only 55 NIH New Innovator awardees in 2009, and she was funded for 5 years to develop state-of-the-art imaging technology that can measure protein complex formation and protein networks in a multiplexed fashion with spatial resolution beyond that of the optical microscopy.

11. How would you like to see the work of the Biological Science and Technology Group develop in the future? What goals would you like to realise?
    The scientific community does not currently understand how to assess either the

functional potential of a biological entity or the root causes of complex observable traits, such as the ability of a microbe to make someone sick or how to synthesize a fuel source from renewable materials. Addressing this challenge lies in deciphering clues present within a DNA sequence, with predicting the function of individual gene products being only the first step. Assembly and modeling of potential gene products, their functions and how they interact within the complicated environment internal and external to a cell will let us answer questions we need to address to achieve our national security mission, such as: "How harmful will a given new microbe be? What are the best ways to detect and contain it? What are the worst effects that may be seen by patients? What is the short list of potential vaccines, anti-microbials or other therapies that would mitigate detrimental effects and/or block infection and transmission?" or "How are complicated polysaccharides broken down in nature? How can we harness these pathways to efficiently generate fuels from renewable sources? Can we improve upon what nature has designed by 10X? 100X?"

We must strive to answer these types of questions through the rapid acquisition, integration, and analysis of multi-dimensional biological data streams to better understand the functional potential of a microbe. The extracted knowledge will provide the actionable information that we require for national-level challenges such as rapid outbreak response, detection of host exposure due to terrorist activities or options for giving our country the energy independence we need to remain secure.

12. Is there any other aspect of your work you would like to discuss?

Roundtable question (editorial feature):

Do researchers feel an increasing need/pressure to disseminate their research to the public? Should all areas of scientific research be made known to the public or are there specific aspects that should most definitely remain private? Where do you draw the line and why? Should more be done to bridge the gap between science and society and why? What would you suggest?