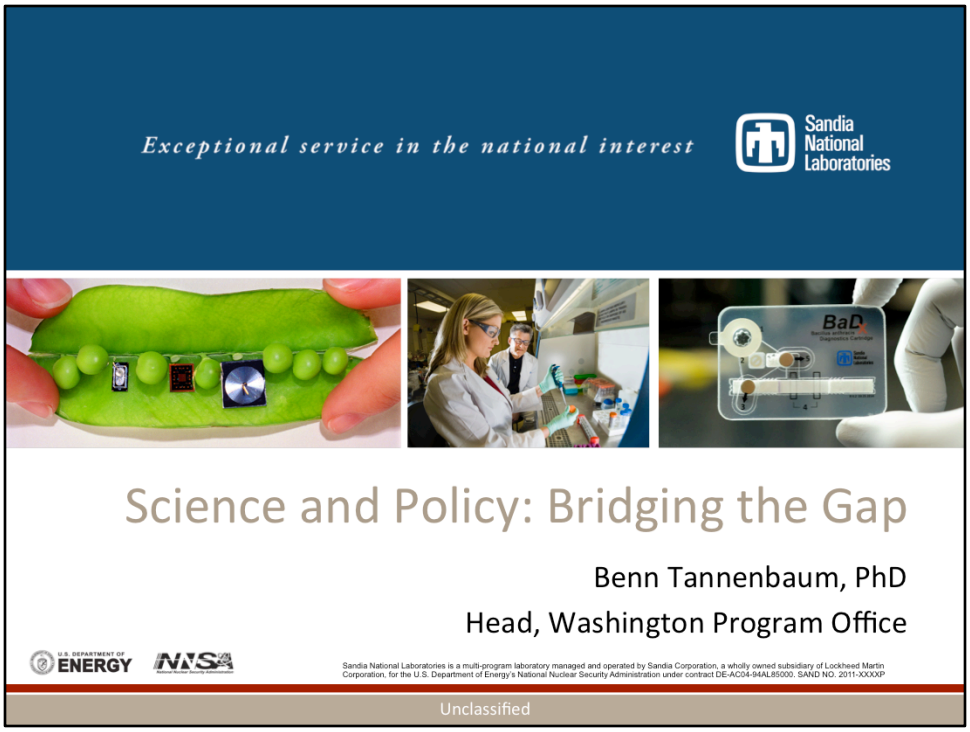
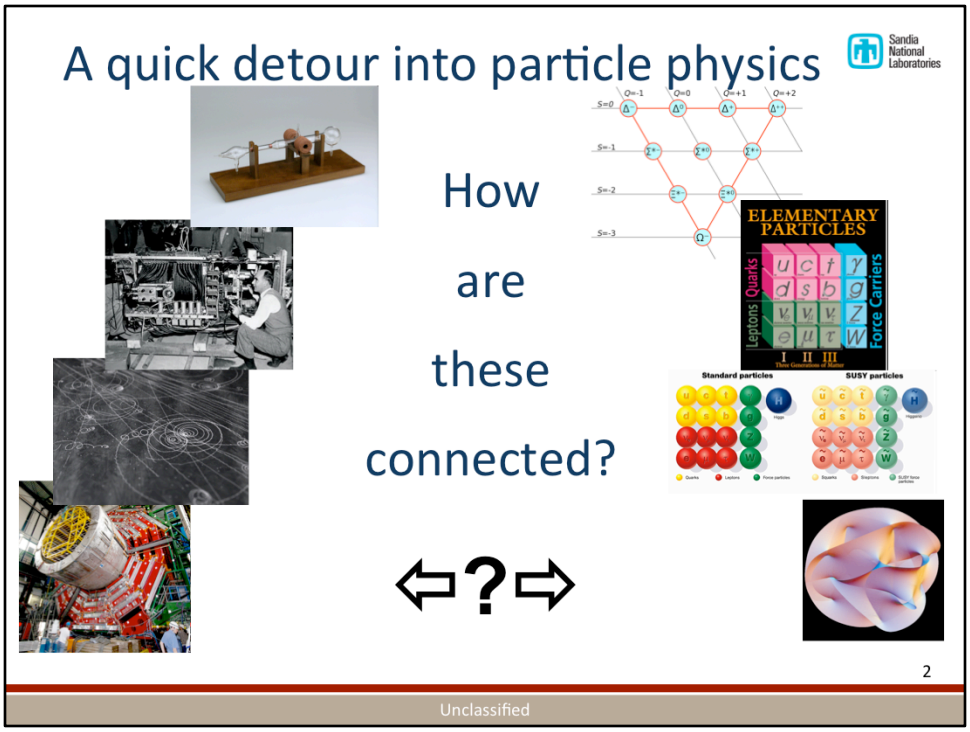


Thank you for that introduction. I'm delighted to be here today, to talk about the intersection of science, policy, and national security. Before I look at this question in the context of systems biology, I want to walk through a few other examples of where important communities didn't effectively communicate and what the consequences were.



As {you can see in my biography, noted in my introduction}, in a past life I was a particle physicist. Particle physics is the study of the tiny components of not just atoms, but nuclei: things with names like quarks, leptons, and bosons. The field got its start with the 1897 discovery of the electron by JJ Chadwick, using a cathode ray tube similar to what you see in the top left picture. Using cloud chambers and watching cosmic rays, many other new particles were found. In the second photo, you see Carl Anderson next to the cloud chamber he used to find evidence of antimatter. The third photo is a picture of a cloud chamber. After some decades, we began to build particle accelerators of various types. These got bigger and bigger, necessitating larger and larger detectors. My dissertation experiment was the size of a nice house; we had some 450 people on the experiment. The CMS experiment at CERN, on which I worked as a post doc, is shown in the bottom photograph. The "C" in the name of that detector is for Compact, because that detector is compact compared to the other large experiment at CERN, which is some 40 meters long and 25 meters tall. Each of these experiments has between 2000 and 3000 authors for every scientific paper. Because these experiments are so large and complicated and the analyses of data undertaken are so long and complicated, you find people specializing in building certain kinds of hardware, writing certain kinds of software and undertaking certain kinds of analyses. And even within a collaboration you find people who are doing things you cannot understand because it is so different from what you do. In many ways, the experimentalists are becoming engineers and computer scientists, perhaps even more so than what might be considered a physicist.

Meanwhile, theoretical physicists tried to understand what the experimentalists were observing. Sometimes the experimentalists were ahead in finding unexplained stuff, and sometime the theorists were ahead in predicting as-yet unobserved things. The upper right diagram shows one of Murray Gell-Man's Eightfold Way charts, which led to the idea that most of these particles were composed of different kinds of quarks. This took us to theories like quantum electrodynamics, quantum chromodynamics, and, eventually, a unified theory named the Standard Model, shown in the second chart on the right. That theory is the best one ever written down, as every experiment ever done has matched the predictions of that theory incredibly well. But we know that the Standard Model isn't complete because it doesn't include some very fundamental things, such as gravity. So the theory community came up with supersymmetry, shown in the third chart, and string theory, shown in the bottom blob. In many ways, the theorists are turning into pure mathematicians.

So who is in the middle? Who interprets what the experiments find (or don't find) in ways that the theorists can compare with their theoretical predictions? Who converts the math produced by the theorists into something for which the experimentalists can search? The people in a relatively newer community of particle physicists, called phenomenologists. They know enough about both of the other two communities to be able to translate between them.

And why did I take this detour? To highlight the dangers of become too specialized, of becoming to far away from other communities on whom you really rely. If you don't know for what you are searching, why build experiments? And if your theories don't have sufficient ties to the real world in order to make observable predictions, how do you know if they are valid?

Let me turn now to nuclear weapons. Nuclear weapons are a fine example of where discoveries in science and technology drove incredible advances in capabilities over just a few decades. The bombs you see near the top are recreations of Little Boy and Fat Man, the two nuclear weapons dropped on the Japanese cities of Hiroshima and Nagasaki, respectively, near the end of the WWII. The top right photo shows a nuclear test just after the war; the bomb had roughly the same yield as those used during the war. Just to give you a sense of scale, the tiny black things you see on the surface of the ocean are captured Japanese warships. Remember, that's one bomb.

As time went on, we went by the adage "when the only tool you have is a hammer, everything's a nail". We had nuclear bazookas, shown in the center photo, and atomic cannons, shown below and to the right of the bazooka. We invented weapons that were the equivalent of millions of tons of dynamite. We trained our troops to fight an atomic war. We built nuclear landmines and nuclear sea mines, nuclear cruise missiles and nuclear depth charges. Each of these weapons and all of this training was in response to a perceived military need, articulated by the US Army, Navy or Air Force. Thinkers in the Pentagon came up with ways to fight wars with nuclear weapons, and scientists and engineers at the national laboratories designed weapons to allow those nuclear wars to be fought. In many ways, the Pentagon viewed nuclear weapons simply as larger, more powerful cousins to conventional munitions.

Over time, we saw the US Army divest itself of its nuclear weapons, and our remaining nuclear forces settle on three main types: land-based intercontinental ballistic missiles, sea-based submarine-launched ballistic missiles, and aircraft-delivered bombs and cruise missiles.

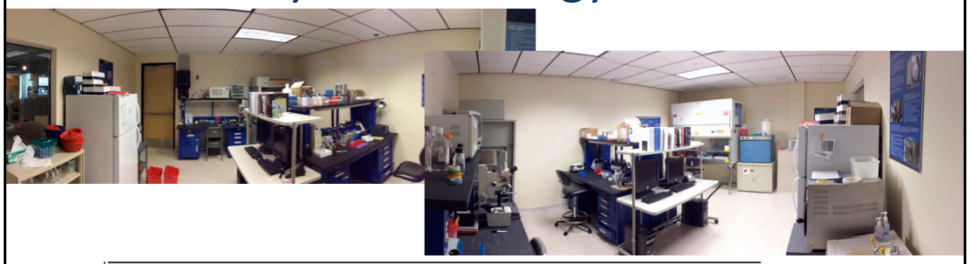
What drove this change? A change in thinking. A realization that nuclear weapons *are* different than conventional weapons. A realization that the damage caused by nuclear weapons was fundamentally different, due to radiation, firestorms, and more, than that caused by conventional weapons. And a realization that the ability to put ordinance on target, from thousands of miles away, was new to warfighting. This was caused by understanding things like Mutual Assured Destruction, first and second strike capabilities, and deterrence theory. Understanding how an adversary was likely to react to an attack on them, given the short response windows. And an understanding that limiting the spread of nuclear weapons was central to US security.

Why did I take *this* detour? To point out that sometimes science and technology get far ahead of a deep understanding of the policy implications of the capabilities they provide.

Images from the NNSA Flickr stream (B-2 dropping B-61 flight test; used under license https://creativecommons.org/licenses/by-nd/2.0/legalcode) and from DefenseImagery.mil (ICBM and SLBM and are not

A look at systems biology

Sandia National Laboratories



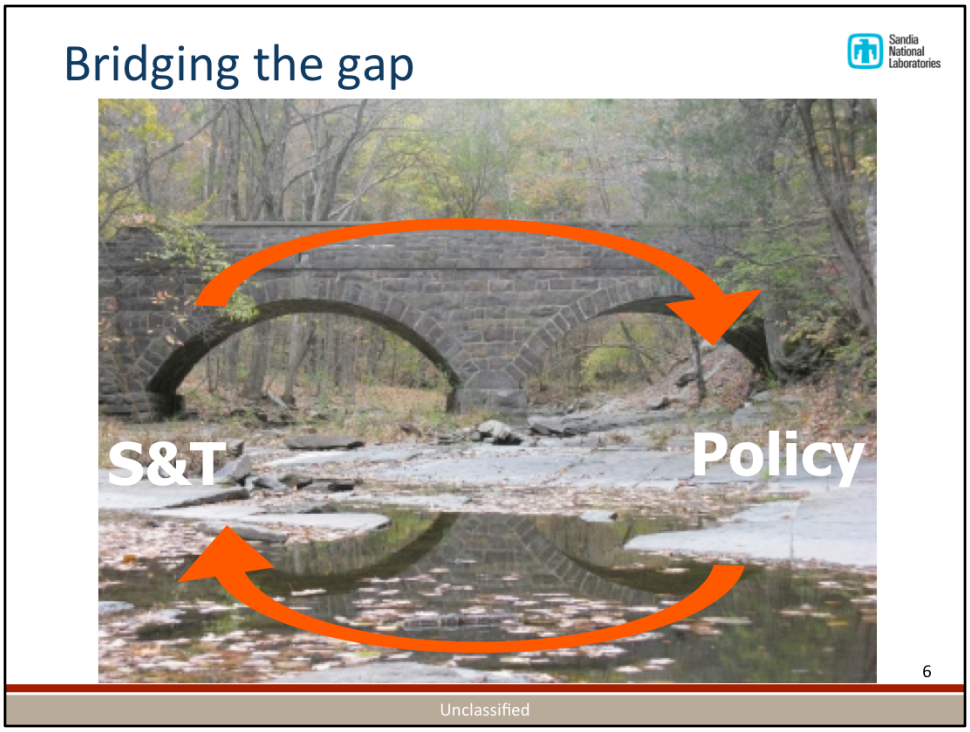
Enzyme[b]	Gene location(s)	Coordinates	Resistance phenotype
NDM-1 (class B)	pNDM-US Tn*125*	122191–123003	Penicillins, cephalosporins, carbapenems, inhibitor-resistant
SHV-11 (class A)[c]	1. pKpn2146b	36313–37173	Penicillins, some cephalosporins, inhibitor-sensitive
	2. Chromosome	2612996–2613856	
CTX-M-15 (class A)	1. pKpn2146b IS*Ecp1*	47130–48005	Penicillins, some cephalosporins, aztreonam,
	2. Chromosome IS*Ecp1*	5407530–5408405	inhibitor-sensitive
TEM-1 (class A)	pKpn2146b Tn2	50827–51687	Penicillins, some cephalosporins, inhibitor-sensitive
CMY-6 (class C)	pNDM-US IS*Ecp1*	72203–73348	Penicillins, some cephalosporins, inhibitor-resistant
OXA-1 (class D)	pKpn2146b ΔIn37	38798–39673	Penicillins, inhibitor-resistant
AAC(3)-IIe	pKpn2146b	41116–41976	Gentamicin, tobramycin, netilmicin, sisomicin
AAC(6′)-Ib (43)	pNDM-US In46	115114–115737	Tobramycin, amikacin, netilmicin, sisomicin
AAC(6′)-Ib (1)	pKpn2146b ΔInTn1331	82745–83350	Tobramycin, amikacin, netilmicin, sisomicin
AAC(6′)-Ib-cr (29)	pKpn2146b ΔIn37	38113–38712	Tobramycin, amikacin, netilmicin, sisomicin, quinolones (low-level)
ANT(3″)-Ia	Kpn23SapB In127	2297711–2298502	Streptomycin, spectinomycin
APH(3″)-Ib (StrA)	pKpn2146b ISCR2	53244–54047	Streptomycin
APH(6)-Id (StrB)	pKpn2146b ISCR2	52408–53238	Streptomycin
Sul2	pKpn2146b ISCR2	54108–54923	Sulfonamides
RmtC	pNDM-US IS*Ecp1*	120100–120945	Aminoglycosides (via rRNA modification)
Sul1	1. Kpn23SapB In127	2299007–2299846	Sulfonamides

5

Unclassified

Let me turn now to biology in general and systems biology in particular. As noted in my biography, I teach a course on nuclear weapons at George Washington University's Elliot School of International Affairs. I tell my students that while nuclear weapons are dangerous and scary, it's bioweapons that keep me up at night. Why? For several reasons. First, nuclear weapons were born classified. By that I mean that all detailed information about the design and manufacture of nuclear weapons has always been classified, limiting access to those who have a demonstrated need to know. Biology, on the other hand, follows the rich scientific practice of publishing everything in the open literature, advancing the frontiers of human understanding. Second, the scale of the infrastructure required to make dangerous things is radically different. To enrich uranium to weapons grade requires buildings full of centrifuges or comparable technologies. To make weapons-grade plutonium requires burning reactor-grade uranium in a nuclear reactor and harvesting the plutonium from the highly radioactive spent fuel using large-scale industrial chemistry. But to make dangerous pathogens requires a much smaller laboratory. The two photos are of a bio lab Sandia assembled for training purposes. While it's not a state of the art lab, one could still undertake fairly sophisticated research here, especially when coupled with resources available via the internet. Note that this lab was assembled for $10,000. It is small and could fit nearly anywhere, requiring only electricity, clean water, and a few other supplies. And remember, too, that today's Nobel Prize-winning research is tomorrow's high school biology demonstration. Third, everything in biology– especially systems biology– is inherently dual-use. Research to make a better delivery system for flu vaccines can be used to make better delivery systems for dangerous pathogens. Sandia, my own laboratory, has done novel research into antibiotic resistance. Rather than trying to find a new antibiotic, our researchers have instead sequenced and published the genome for *Klebsiella pneumoniae* in order to learn which enzymes and genes grant resistance in hope of finding ways to turn off that resistance. If I can turn off resistance in one pathogen, what is to prevent me from conferring antibiotic resistance to other pathogens?

Images courtesy of Rodney Wilson, Sandia National Laboratories. Table taken from *Resistance Determinants and Mobile Genetic Elements of an NDM-1-Encoding* Klebsiella pneumoniae *Strain by Hudson et al.* DOI: 10.1371/journal.pone.0099209



So what is my message? I am not suggesting that research into systems biology stop. I'm not suggesting that we don't publish research results, either positive or negative, as we must continue to make advances in protecting and promoting human health.

What I am suggesting is two-fold. First, as Ruth Berkelman and James Le Duc suggested in their recent editorial in *Science* magazine, we need to have ethics training for scientists as part of their regular graduate training– if not undergraduate education– to create a culture of responsibility. As they ask, "why are scientists required to understand the individual risks to participants in a clinical trial but not required to have ethical training related to the potential risks of research to the public?"

Second, being here at this meeting is just the first step. While some of you frequently and regularly engage– or are-- policy makers on this important topic, we need more of you. We need more scientists who are policy- and politically-literate, so they can speak to policy makers in Congress and executive branch agencies like DHS and NIH. Just like particle physics experimentalists and theorists, scientists and policy makers speak fundamentally different languages. Policy makers will never learn our language, so we must learn theirs in order to bridge the gap between science and policy. Most members of Congress either directly know someone or have constituents afflicted with this or that disease and will support funding into fundamental life science research. But only rarely are they aware of the potential risks of such research. It is up to us, as a community of scientists, to engage them on this important topic. Because if we don't, there is a very strong chance that regulations will be imposed upon us and we will most likely not be happy with those regulations.

I thank you for your attention and look forward to the discussion.

Image from http://www.freedigitalphotos.net/images/Bridges_g298-Stone_Arch_Bridge_p1313.html and is copyright-free.