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maps in terms of cognition beyond physical space; his main theme was that animals and humans have a 'map-like' organization of experience that supports expectancies and inferences (rather than simple stimulus–response habits). I would like to ask Tolman how his notion of a cognitive map should be interpreted, given what we now know about the hippocampus.

What is the best advice you've been given? Agranoff told me: choose a hypothesis to explore, outline the stepwise series of experiments that would test ever more risky predictions of your hypothesis, and then pursue the last of those experiments first. Once the riskiest predictions are confirmed, the earlier experiments are just 'clean-up'.

What's your favourite experiment? My favourite is not a single experiment, but the combination of recent experiments in comparative neurobiology that have provided insights into how the hippocampus supports memory, including how space is involved in memory in animals and humans. One set of experiments provides unambiguous evidence that the hippocampus is critical for memory performance in animals that mimics fundamental properties of human conscious recollection. Another set of experiments revealed that hippocampal neurons encode successive moments in temporally structured experiences, consistent with the characterization of recollections as organized by the flow of events in time. And yet another set of experiments has revealed that hippocampal neuronal populations systematically bind related events in space and time. The combined findings suggest that the hippocampus creates a 'memory space', an associative network organized by physical space, the flow of time, and potentially other relevant dimensions by which events are related (which is what I believe Tolman meant by his notion of a cognitive map).

What has been your biggest mistake...? I have made lots of mistakes. My biggest failure is my inability to convince my very clever colleagues who study hippocampal function in spatial navigation that they are on the wrong track and should instead contribute their considerable expertise to unravelling the biology of memory.

Do you believe there is a need for more crosstalk between biological disciplines? My desire to bridge between the cellular–molecular and behavioural–cognitive levels of memory is hampered by a lack of crosstalk between practitioners in each discipline. I believe crosstalk could generate a language for describing the circuit or network information processing mechanisms by which cellular activity ultimately supports cognitive functions. We all too often refer to cells that 'code' a place, a memory, or a feeling, whereas cells do no such things. We need to identify the basic information processing functions that cells and circuits do perform, and show how these basic functions enable the expression of complex cognitive phenomena we experience as places, memories, and feelings.

What do you think are the big questions to be answered next in your field? As reflected in President Obama's BRAINs initiative, we need new approaches to monitoring, manipulating, and analysing neural populations that will allow us to understand how brain networks, circuits, and systems perform functions that support higher order cognition. Within the field of memory, we need to scale up our capacity to record, interpret, and manipulate the activity of large populations of neurons both within the hippocampus and among the full system of brain structures with which the hippocampus interacts. Combined with a deeper knowledge about the basic elements of information processing performed by these areas, we then can work towards a comprehensive understanding of how memory works.

If you could ask an omniscient higher being one scientific question, what would it be and why? Did you make the brain so complicated just to entertain me or to drive me crazy?

Center for Memory and Brain, Boston University, 2 Cummington Mall, Boston, MA 02215, USA.
E-mail: hbe@bu.edu

Quick guide

Type VI secretion system

Dor Salomon* and Kim Orth

What is it? The type VI secretion system (T6SS) is a macromolecular protein secretion apparatus that is used to transfer proteins into an adjacent recipient cell in a contact-dependent manner. The T6SS is structurally similar to a contractile phage tail but in a reverse orientation: whereas the phage attaches to a bacterial cell from the outside and penetrates the membrane to deliver genetic material into the cell, the T6SS is assembled inside the cell and is used to deliver proteins out of the cell and into the recipient.

Where is it found? The T6SS is present in ~25% of the Gram-negative bacteria sequenced to date. Remarkably, up to six different T6SSs can be encoded within a single bacterial genome. Although it has mostly been studied in *Vibrio* and *Pseudomonas*, it is also found in many other bacterial species, including animal and plant pathogens, commensals, and environmental strains that occupy a plethora of habitats.

How does it work? There are 13 core components that make up the minimal set required to assemble a functional T6SS (Figure 1). It is composed of an inner tail tube that is made of hexameric rings of a protein called Hcp that stack on each other. This inner tube is capped with a spike complex made of a trimer of VgrG proteins and a PAAR repeat-containing protein that sharpens the tip of the spike. The tail tube is engulfed within a contractile sheath-like structure that is assembled by two proteins, TssB and TssC. Interestingly, the components of the tail tube structurally and functionally resemble those of contractile bacteriophage tails. A membrane complex, composed of the subunits TssL, TssM and TssJ, spans the bacterial periplasm from the inner membrane to the outer membrane and anchors the tail tube to the membrane during assembly of the T6SS apparatus. During secretion, the sheath contracts and propels the inner tube outside of the cell and into an adjacent recipient cell, like an arrow. After

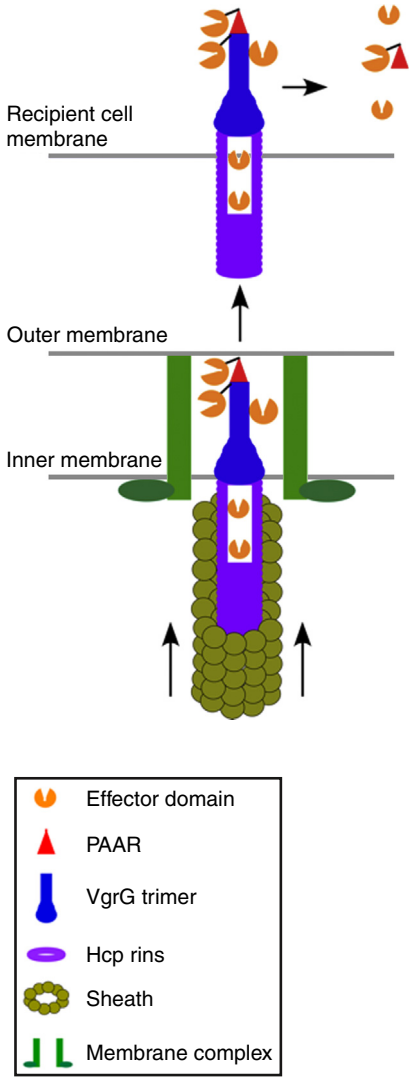

Figure 1. Schematic representation of the T6SS. An inner tube made of hexameric rings of Hcp is capped with a spike complex made of a VgrG trimer and a PAAR repeat-containing protein. This inner tube, decorated with effector proteins, is propelled out of the cell and into an adjacent recipient cell by the contraction of the sheath-like structure that engulfs the inner tube. The tube is anchored to the membrane by an envelope-spanning membrane complex.

secretion, the sheath is disassembled and recycled to allow the core components to be used again. The proteins secreted by the T6SS are called effectors. These effectors decorate the tail tube either as domains fused to the secreted structural T6SS components (Hcp, VgrG, and PAAR) or as separate proteins that bind to these structural components. The effectors are thought to be delivered with the inner tube into the recipient cell.

What does it do? The T6SS was originally described as a bacterial virulence mechanism against eukaryotic hosts. However, more recent findings show that most T6SSs are actually used as antibacterial determinants during interbacterial competition and are used to kill competing bacteria, suggesting that the T6SS can enhance environmental fitness for the attacking bacteria. There are also reports suggesting that in some bacteria the T6SS plays a role in biofilm formation, adhesion to host cells, or even in the maintenance of intracellular pH homeostasis. Recently, it was shown to act as a driver of genetic diversity by allowing bacteria to acquire DNA from dead competing bacteria during interbacterial competition. Remarkably, recent reports indicate that T6SS effectors with antibacterial cell wall degrading activities have been acquired by eukaryotes, via horizontal gene transfer from bacteria, and used to augment eukaryotic innate immune systems.

How is it activated? The T6SS appears to be tightly regulated in most bacteria, and in cases where there are multiple T6SSs encoded in a single genome, each is differentially regulated. Many environmental conditions and cues have been found to regulate the system, such as temperature, salinity, iron concentration, pH, sub-inhibitory concentrations of antibiotics, and a density-dependent regulatory mechanism known as quorum sensing. In many cases, the cues that activate the T6SS are found in a habitat that is occupied by the bacterium and in which activation of the system provides an advantage. Moreover, physical signals such as surface sensing and membrane perturbations can activate some T6SSs. For example, sensing of kin cell lysis caused by a T6SS-mediated attack or type IV secretion system-mediated conjugation from a neighboring bacterium can activate an antibacterial T6SS in *P. aeruginosa.*

What effectors are secreted by the T6SS? Generally, effectors can have either virulence activities against eukaryotic cells or antibacterial activities. Virulence activities described for T6SS effectors include actin crosslinking and ADP ribosylation. Antibacterial effectors include nucleases, pore-forming toxins and peptidoglycan hydrolases. In addition, an interesting family of phospholipases was first described to have antibacterial activities, but some members were later shown to also mediate virulence against eukaryotic cells using the same enzymatic activity. Two classes of polymorphic T6SS effectors exhibiting various toxicities were also described; one contains Rhs repeats and the other contains a MIX motif. Rhs- and MIX-containing effectors have variable carboxy-terminal toxin domains with either antibacterial or virulence activities, and are widespread among bacterial pathogens.

How do cells protect themselves against T6SS attack? T6SS effectors that possess antibacterial activities are produced in conjunction with a cognate immunity protein to protect the cell against self-intoxication. The immunity protein physically associates with the effector to inhibit its deleterious activity. The gene encoding the immunity protein is found adjacent to the effector gene in the same operon as a bicistronic unit. Thus, when there is an attack of one bacterial strain against another, the attacker does not kill its kin.

Why is the T6SS important? Because in some bacteria the T6SS is a major virulence determinant, understanding how it works and identifying the toxic effectors it can deliver into the host cell would help us to protect ourselves against the pathogen. Moreover, the T6SS appears to be a major determinant in interbacterial interactions and a promising reservoir of toxins with antibacterial activities that may illuminate novel targets for antibacterial treatments.

Where can I find out more?

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Department of Molecular Biology, University of Texas Southwestern Medical Center, Dallas, TX 75390-9148, USA.
*E-mail: Dor.Salomon@UTSouthwestern.edu

