THE HARTWELL FOUNDATION

2013 Individual Biomedical Research Award

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Promoting Nervous System Self-Repair to Treat Peripheral Neurodegeneration and Demyelination in Children

Development of a functional and efficient nervous system requires the orchestrated migration of nerve fibers (axons) from the brain and spinal cord out into the periphery, where the axons connect to the tissues and organ systems that provide sensory and motor (muscular) control for the body. Most axons are wrapped in a special coating called myelin, which acts like the plastic insulation coating on an electrical wire, allowing nervous system signals to travel much more effectively than if the coating were not there. This myelin coating originates from the outgrowth of specialized cells which support the health of the axon. In the central nervous system (CNS), oligodendrocytes perform this function and in the peripheral nervous system (PNS) Schwann cells are responsible for making myelin. If the myelin sheath is abnormal or damaged (myelinopathy) the nerves malfunction, degenerate and ultimately die. The progressive loss of myelin along peripheral nerves with loss of sensation and limb control often leaves children wheelchair bound before the age of three. Myelinopathy occurs in muscular dystrophy, multiple sclerosis and traumatic injury to the spine/brain. Unfortunately, no existing treatment addresses the damage to the myelin sheath. With no cure, existing therapeutic interventions include physical therapy, orthopedic devices, surgery and pain-killing drugs to help cope with the disabling symptoms of these diseases. In 2013, Sarah discovered that ablation of Schwann cells at the junction between the CNS and PNS promotes the migration of oligodendrocytes from the spinal cord to myelinate peripheral axons. She hypothesizes that this observation can be interpreted as evidence of nervous system self-repair and proposes that if self-repair can be harnessed, it could be used to treat childhood diseases that adversely affect peripheral nerve myelination. To test her hypothesis, she proposes to develop a zebrafish model to characterize cell-cell interactions that occur between oligodendrocytes and Schwann cells along the path of motor axons (responsible for muscle control). Using high-throughput drug screening in the zebrafish, she will first identify compounds that promote the recruitment of healthy oligodendrocytes to peripheral motor axons and then evaluate them in a mouse model of a genetic myelinopathy. If Sarah is successful, targeted drug therapy will make it possible to facilitate the migration of healthy myelinating cells into the PNS to overcome the loss of myelin observed in peripheral myelinopathies. Enlisting healthy CNS cells to fulfill a role lost by their PNS counterparts will reverse the progressive neural and muscular degeneration that accompanies these diseases and thereby improve the quality of life of affected children.