subjects were treated with neratinib, an irreversible pan-HER tyrosine kinase inhibitor (TKI) that was approved by the FDA in 2017 for the treatment of early-stage HER2-positive breast cancer. Among enrolled subjects, there were 31 distinct types of *HER2* mutations and 11 unique *HER3* mutations.

The authors found that the greatest objective response rates were seen in breast, cervical and biliary cancers and with tumors that contain kinase domain missense mutations, while no responses were observed in bladder or colorectal cancers. Similar to the vemurafenib study, these results reiterate that the biology and therapeutic relevance of mutations in various cancers can be different. In addition, they found that the efficacy of neratinib in HER3-mutant cancers was not predicted by preclinical models. Despite experimental data suggesting that mutations in *HER3* can drive and sustain the growth of cancers in a manner analogous to that of *BCR-ABL* in chronic myelogenous leukemia, no responses were observed in HER3-mutant tumors. These points highlight that real data from actual subjects are the most important arbiter of the clinical relevance of tumor mutations. It should be noted, however, that a key assumption of these studies is that the sensitivity of different tumors with various mutations to neratinib is the same regardless of mutation type, as neratinib was given only at a fixed dose (the recommended dose). Pharmacodynamic data showing whether neratinib at 240 mg daily led to steady-state concentrations of drug able to fully inhibit the activity of the mutant kinases were not presented. Finally, the authors sought to identify genomic modifiers of response through broader genomic characterization of tumor-derived DNA. Not surprisingly, the authors found that tumors are genetically heterogeneous and that mutations co-occurring in other cancer genes may impact responses. Future disease-specific studies will be needed to define these associations better.

In addition to the SUMMIT study, investigators have also recently pioneered 'multi-basket' studies, whereby multiple molecular alterations are concurrently assessed in multiple disease types. For example, in the Phase IIa MyPathway study, Hainsworth and colleagues[4] evaluated the efficacy and safety of four different currently approved regimens of targeted therapy in 251 subjects with 35 different tumor types. The MyPathway study produced meaningful responses in several refractory solid tumor types not currently approved for these agents and provided new clinical insights into the biology of specific molecular alterations.

Taken together, the advent of new master protocols, such as the ones discussed above, should fulfill three missions. First, results will address the limitations of preclinical models for predicting clinical outcomes as described. Second, outcomes may lead to new biological insights, enabling further bench-to-bedside research. Finally, data from such studies will be important contributions to a comprehensive tumor gene–response outcome database that can guide the rational use of targeted therapies in patients with cancer. Multiple initiatives to create such a database are already underway. For example, the American Association for Cancer Research (AACR) Project Genomics Evidence Neoplasia Information Exchange (GENIE) is a multiphase, multiyear, international data-sharing project that catalyzes precision oncology through the development of a regulatory-grade registry, aggregating and linking clinical-grade cancer genomic data with clinical outcomes from tens of thousands of patients with cancer who were treated at multiple international institutions[5]. Such efforts, coupled with sound statistical approaches, should improve clinical decision-making, particularly in the case of rare cancers and rare variants in common cancers, ultimately helping patients receive the most appropriate, individualized therapies.

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Transplanted neural progenitors bridge gaps to benefit spinal cord–injured monkeys

Steven A Goldman

Human neural progenitor cells have been grafted successfully into rhesus monkeys with spinal cord hemisection, resulting in anatomic integration and improved neurological function.

In the central nervous system (CNS), the spinal cord is a critically important conduit for sensory and motor signals. Relatively small spinal anatomic lesions can cause irreparable harm, as the ascending sensory and descending motor and autonomic pathways, as well as their connections to local inputs and outputs at each spinal level, lie within just a few centimeters of one another. Furthermore, most of the spinal cord's length lies within a tight cylindrical space so that any swelling of the cord tissue after injury can lead to squeezing of the affected cord to the point of vascular compression. The collapse of spinal venous drainage, accompanied by the attendant feed-forward increase in intraspinal pressure, can lead to an eventual disruption of arterial flow. As a result, traumatic spinal cord injury (SCI) can quickly evolve into spinal ischemia, with infarction and the tragic outcome of irreversible tissue loss. The ability to intervene in this process has thus far proven limited; to date, no medical therapies exist for SCI, and no surgical treatments have proven effective, save for decompressive laminectomy in very select cases. As a result, even though spinal neural pathways are among the most well-understood circuits in neurobiology, that understanding has not yet translated to effective strategies for either their rescue or repair after traumatic injury[1]. In this issue of *Nature Medicine*, Tuszynski and colleagues[2] report the amelioration of both tissue injury and

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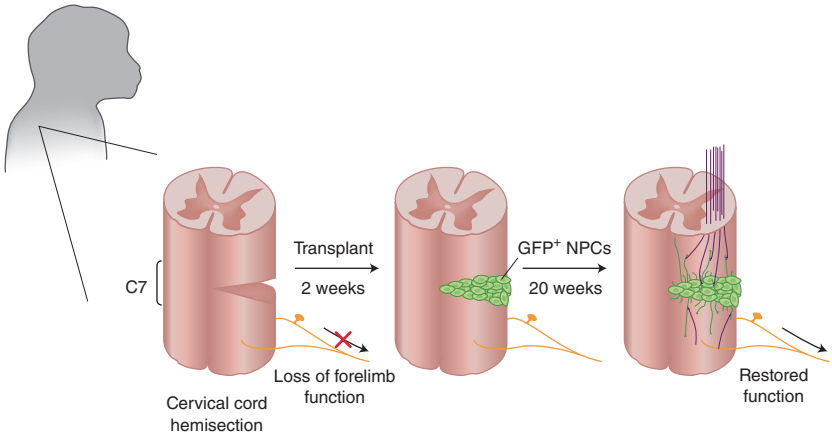

Figure 1 Transplant of human NPCs into injured monkey spinal cord results in a successful graft. Tuszynski and colleagues[2] transplanted human neural progenitor cells (NPCs) labeled with GFP into the hemisected monkey spinal cord, a model that mimics severe human SCI. They found that after 20 weeks, donor neurons (green) extended fibers into the host spinal cord while receiving inputs from the host (yellow), enabling the graft to serve as a functional bridge across the injury site and resulting in partial restoration of motor function. Thanks to A. Benraiss for figure composition.

neurological deficits after SCI in rhesus monkeys through use of human neural progenitor cells delivered locally to the site of injury.

In this study, Tuszynski and colleagues[2] build on recent studies that have evaluated the use of human neural progenitors in rodent SCI[3,4] to assess the efficacy of human neural progenitors in nonhuman primates. In their earlier studies in rodents, Tuszynski and colleagues[5] reported that spinal NPCs proved better able to support corticospinal tract ingrowth in lesioned rodent spinal cord than analogous forebrain-derived cells. They also showed that the axons of newly produced neurons from implanted NPCs can project far into adult tissue, as has also been shown in rodent models of induced neurogenesis[6]. Thus, it seems that axons can be extended in the adult CNS by newly developing neurons, unconstrained by the inhibitory signals that might otherwise suppress axonal regeneration by resident mature neurons. However, the neuroanatomy of the human spinal cord differs greatly from that of rodents, so much so that nonhuman primate models are required to further assess the therapeutic potential of neural progenitor grafts. Marmoset monkeys were first used successfully for this purpose[7] in studies that suggested the utility of moving from rodents to primates, which have a more human-like size and neuroanatomy. Old-world monkeys, such as the rhesus macaque, share the bulk of the major tracts, patterns of connectivity and functional relationships that characterize the human spinal cord; as such, Tuszynski and colleagues[2] chose to use the rhesus macaques with SCI in their experiments.

The investigators carried out hemisection of the cervical spinal cords of rhesus macaques to model an especially severe form of human SCI, which may occur with penetrating injuries of spinal cord or traumatic displacements of vertebral column. Two weeks later, they grafted human NPCs derived from early human fetal spinal cords into the lesion sites (**Fig. 1**). The authors used early NPCs derived from human spinal cord as their donor cells; their past studies had indicated the importance of using spinal progenitors for this purpose instead of the brain-derived cells used in many other past studies of neural stem cell grafts in SCI. In addition, they had previously reported that implanted human donor cells matured slowly in the recipient spinal cord[3]—mimicking the prolonged maturation of human neurons and glia during human gestation—and so they knew to allow longer recovery times before evaluating the transplanted monkeys. Combining these elements in the design of their present study, they found that implanted human spinal NPCs proceeded to differentiate as neurons and glia—the latter mostly as astrocytes—as far out as 9 months after transplant. They also observed that there was little migration of the NPCs from their transplant sites. This observation distinguished NPCs from their closely related glial progenitor cells, an alternative therapeutic cell type that readily migrates widely throughout the CNS and is hence appropriate for potentially treating many disease targets yet lacks the neuronal production capability of neural progenitor cells[8].

Recovery from SCI is dependent upon the re-establishment of appropriate neuronal connectivity. Tuszynski and colleagues[2] discovered that the newly developing neurons that arose from transplanted neural progenitors extended axons both rostrally and caudally from the graft site. Although a large number of axons penetrated the adjacent spinal parenchyma, most extended no more than 2 mm. Nonetheless, a small number of donor axons appeared to extend as far as 5 cm, exhibiting long-distance projection through the descending lateral corticospinal tracts.

Given the limitations of sample size inherent in working with primates, the authors could not assess the relative contributions of the different donor-derived axons to functional improvement. Nonetheless, the monkeys did show a restoration of forelimb functions, such as object manipulation, beyond what would typically be expected following surgical hemisection. A set of four lesioned monkeys whose grafts were unsuccessful manifested little functional change beyond their first perioperative month, whereas five successfully engrafted monkeys that were tested for as long as 9 months all showed some degree of progressive improvement. These improvements included partially restored segmental forelimb function that was accompanied by improved long-tract function and locomotion. Notably, as important as the investigators' five successful transplants were, their failures in this study were equally informative, as they identified the importance of draining the lesion site of cerebrospinal fluid and of suspending the donor cells in a growth-factor-laden fibrin matrix as critical steps in ensuring successful donor cell engraftment.

On the basis of these promising data, the authors proposed that neurons that arose within the grafts established connections with ingrowing transected fibers while projecting their own axons out into the host spinal cord. They postulated that in doing this, the grafts formed multisynaptic bridges through which ingrowing axons could use graft-derived neurons as functional intermediaries used to communicate with their distant targets. As such, those monosynaptic pathways lost to SCI—including those of both ascending sensory and descending motor tracts—might be restored through polysynaptic, graft-mediated relays. Although speculative in regard to these monkeys, this concept of the grafted cells providing a neuronal bridge for restoring long-distance, polysynaptic connectivity has been advanced in a number of studies of rodent SCI[5,9–11], most recently with the use of rabies tracing to more precisely infer the synaptic relationships of host and donor neurons[12]. In these rabies-traced rodent spinal cords, the donor neurons indeed appeared to serve as synaptically coupled bridges between the proximal and distal portions

of transected cord. Further studies would benefit from ablating the grafted neurons to prove that the motor improvement in monkeys depended directly on the engrafted cells and their vector-specific connections with the host.

SCIs are varied in nature, as are their clinical presentations and prognosis; no two are the same. A patient with incomplete and nontransective injury can improve over time, and this improvement may be as significant as it is unpredictable. But if there is one common theme, it is that patients with frank transections or severe contusions with tissue cavitation are left with permanent injuries with severe impairment and little improvement over time. These patients are thus likely to be the greatest beneficiaries of a neural-progenitor-based treatment strategy and are the first in whom it is likely to be assessed. By convincingly demonstrating that transplant-based reconstruction of neural circuits in the injured spinal cord can be effective and in doing so in nonhuman primates, Tuszynski and colleagues[2] have thus significantly advanced the cause of neuronal replacement therapy for spinal repair and have brought this exciting strategy one step closer to the clinic.

COMPETING INTERESTS
The author declares no competing interests.

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A molecular mechanism governing memory precision

Josue Haubrich and Karim Nader

A key molecular mechanism has been identified that dictates whether memory will maintain or lose its details over time and that is relevant in post-traumatic stress disorder and dementia.

Memories enable people to recollect events from the past to both plan for the future and properly guide their behavior in the present. However, memories change over time, often losing details. Minor loss of memories or details is common and usually not cause for alarm—however, in many cases the erosion of memory details can reach pathological levels that can significantly decrease quality of life. This extreme dysfunction can occur with pathological memory decline during aging and also as a symptom of post-traumatic stress disorder (PTSD) in the form of intrusive flashbacks that occur even in contexts unrelated to trauma[1]. Previous studies in rodents have linked memory imprecision with a gradual reorganization of the brain circuits supporting that memory[2]. In a new study, Sahay and colleagues[3] unveiled a critical mechanism governing both memory reorganization and the maintenance of its details over time.

The hippocampus is critical in forming, maintaining and accessing explicit memories. Over time, memories in the hippocampus may undergo a process called systems consolidation, through which memory becomes gradually independent of the hippocampus and dependent on cortical circuits[4]. It is thought that this consolidation might also play a role in precision of memory recall[2]. In addition, converging evidence suggests that dentate gyrus cell (DGC) connectivity in the hippocampus is also important for memory precision[5–7] and that this connectivity guides memory maturation in cortical networks over time[8]. Improper changes in this circuit may help explain aging-related memory loss[9] and excessive fear associated with PTSD upon unclear memory recall[10]. The DGC sends excitatory projections—called mossy fibers—to pyramidal neurons in the hippocampus CA3 area. Importantly, mossy fibers can also connect to GABAergic interneurons, which in turn inhibit the pyramidal neurons in CA3. This unidirectional circuit, in which a common projection simultaneously activates both inhibitory interneurons and excitatory pyramidal neurons to varying degrees, dictates the CA3 activation pattern and is thought to mediate complex tasks such as pattern separation—the process through which memories are stored as unique representations—and completion—the process through which an experience is recalled when a component of that memory is activated (such as by a specific location)[5,7]. The uniqueness of this DGC–CA3 circuit in regards to its relationship to precise information processing and time-limited engagement in memory recall led the authors to hypothesize that there must be mechanisms linking the DGC–CA3 engagement in memory and the maintenance of details over time.

The authors trained mice to associate a specific context with a foot shock and later tested recall in these mice by placing them back in the original surroundings in which they received the shock or in a new context with distinct features in which they never received a shock (**Fig. 1**). When the authors conducted a test 1 day after training, mice easily discriminated between contexts by showing fear only in the context that they were trained to associate with being shocked; however, 16 days after training, the mouse memory became imprecise, and mice began to show fear in the context not associated with shock. The authors used genetic labeling to identify the DGCs participating in memory and found that, compared to untrained mice, trained mice had DGCs that displayed increased synaptic contacts with both CA3 pyramidal neurons and inhibitory interneurons 1 day after training when memory was precise; however, when memory later became generalized, these contacts returned to the untrained baseline levels. The authors identified a molecule localized in DGC–interneuron synapses called actin-binding LIM protein 3 (ABLIM3), the levels of which decreased when mice were learning to associate context with shock. They found that experimentally reducing levels of ABLIM3 in these synapses resulted in increased DGC–interneuron connectivity and in turn enhanced inhibition onto CA3 neurons. Thus, ABLIM3 is able to promote DCG recruitment of inhibition onto CA3.

Next, the authors assessed ABLIM3's role in memory. Optogenetic activation of DGCs involved in memory promoted precise memory recall in the mice when conducted at 2 days, but not 10 days, after learning, showing that DGC engagement in memory fades over time. However, experimentally reducing levels of ABLIM3 prolonged DGC engagement, promoting recall even 10 days after learning. To assess the effect of prolonged engagement of DGCs, as induced by downregulation of

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