and blocking its function prevents metastasis. POSTN recruits Wnt ligands and thereby increases Wnt signaling in cancer stem cells. We suggest that the education of stromal cells by infiltrating tumor cells is an important step in metastatic colonization and that preventing de novo niche formation may be a novel strategy for the treatment of metastatic disease.

The data describe novel insights both into the “seed” and the “soil.” Cancer stem cells or tumor initiating cells are required for the original colonization of the target organ, and their exclusion from xenografted cells leads to decreased metastatic efficiency. Interestingly, after the cells of arrive at the target organ, they proliferate during the initial growth phase of the tumor and are responsible for cellular expansion. During this period they exhibit a greater than usual fraction of the tumor, functioning to fuel tumor expansion. From the perspective of the “soil,” these metastatic cancer stem cells induce expression ofstromal proteins that facilitate colonization by making the target organ’s molecular and cellular ecosystem more inhabitable. The scientific insights presented in this article could most intriguingly be applied to the brain microenvironment in the context of brain metastasis. Neuroscience remains in its relative infancy and with its further elucidation opportunities will arise to treat brain tumors not only by targeting the tumor itself, but also by exploiting the most complicated biological milieu within which they grow—the brain.

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A Novel Target for Ischemic Stroke Therapy: Pannexins

Targeted therapies to limit the death of brain tissue in ischemic stroke remain an intense area of research. The current armamentarium of the neurologist and neurointerventionist is limited to tissue plasminogen activator (tPA) and mechanical thrombolysis. Although these therapies strike at the root cause of ischemic stroke, they offer little in the way of true neuroprotection. Neuroprotective agents in ischemic stroke and other diseases are a holy grail but despite numerous clinical trials, only one agent is in use today—riluzole for amyotrophic lateral sclerosis. Continued evolution in our understanding of how ischemia actually kills neurons will inevitably lead to the generation of new therapies. One intriguing possibility is the combined use of thrombolitics and a yet to be identified neuroprotective agent to treat acute stroke.

Pannexins form large, non-selective membrane pores that connect the cytoplasm to the extracellular space. Bargiolas et al, in a recent report from Germany, found evidence that pannexin channels have a role in ischemic neuronal death (Bargiolas P, Krenz A, Hormuzdi SG, et al. Pannexins in ischemia-induced neurodegeneration. PNAS. 2011; 108(51):20772–20777). To study how pannexin channels influence the fate of ischemic neurons, these authors created pannexin knock-out mice. Other investigators had shown that channels both electrophysiologically and pharmacologically similar to pannexins opened in response to oxygen and glucose deprivation. To evaluate this, cultured primary cortical neurons from these knock-out mice were loaded with calcine green dye and their fluorescence was monitored under differing metabolic conditions. With no disruption in cellular metabolism, fluorescence remained stable. However, after administration of sodium cyanide, to uncouple mitochondrial respiration, a steady decrease in fluorescence was observed. This was not due to cell membrane disruption, as there was no increase in the concentration of lactate dehydrogenase in the culture medium. Moreover, pretreating the neuronal cultures with an inhibitor of pannexin channels blocked the decrease in intracellular fluorescence induced by sodium cyanide. The experiments established that pannexin channels were responsible for the passage of material from the cytoplasm to the extracellular space following metabolic disruption.

To study the role of ischemic neuronal death in vivo, middle cerebral artery occlusions were performed in both control and knock-out pannexin mice. The mice were evaluated for neurological deficits both before and 24 hours after middle cerebral artery occlusion. Using the corner test, in which a greater deficit involves a mouse turning more often toward the affected side during walking, knock-out mice had a significantly decreased tendency to turn toward the affected side when compared to wild-type mice. In a second neurological test, the latency test (a greater latency to movement implies a greater neurological deficit), pannexin knock-out mice showed a trend toward decreased latency to move. Finally, infarct volumes were measured after the middle cerebral artery occlusions. In pannexin knock-out mice, infarct volumes were reduced by 40% when compared to control animals. Mice harboring incomplete pannexin knock-outs were not protected from middle cerebral artery occlusion.

These findings implicate pannexin channel opening in the series of events leading to neuronal death in brain ischemia. However, what remains to be discovered is the mechanism by which pannexin channels are triggered to open. The authors suggest several possible triggers including elevated extracellular potassium concentrations, reactive oxygen species, or cleavage of pannexin 1 protein by caspase 3, an important mediator of apoptosis. Although nonselective pannexin channel inhibitors have protective effects in stroke models, they also inhibit stroke-protective connexin channels. Thus, highly selective pannexin channel inhibitors should be identified and pursued as potential neuroprotective agents for acute stroke therapy.

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The Neurosurgeon’s Role in Integrated Health Systems

Today’s healthcare industry is like the childhood game of musical chairs, where all the players find themselves jockeying for a dwindling number of available seats—and hoping to win a prize. Those still seated are forming integrated health systems in which hospitals, insurers, physicians, employers, and patients align to meet healthcare needs through collaboration, shared risk and a focus on reigning in costs while insuring higher quality. Neurosurgeons need to pay attention to the trends or risk losing their position in the newly developing healthcare arena.

In a thought-provoking article in The Wall Street Journal, “The Future of U.S. Health Care: What Is a Hospital? An Insurer? Even a Doctor? All the Lines in the Industry Are Starting to Blur,” writer Anna Wilde Mathews describes these changes and how they are playing out among stakeholders. The author explains that hospitals in many cases are merging into large systems, building vast physician networks and excluding insurance middlemen from negotiations with employers.
Insurers, for their part, are purchasing healthcare providers or seeking cooperative deals that allow them to share health coverage risk, while employers are beginning to give their workers incentives that ultimately cut insurance costs.

According to Mathews, the overall picture is one of integration, in which economics are driving stakeholders to join forces to survive—and potentially prosper. Specialty care, including neurosurgery, is necessarily part of the equation and the shifts in healthcare delivery will require active engagement in the process.

Neurosurgeons, for example, will have to determine which model of healthcare delivery will work for them, whether they become hospital or health plan employees, affiliate with an integrated health system, accountable care organization or select independent solo or group practice. Whatever their decisions, the roles and responsibilities will surely shift, as well.

Figure. Double-knockout Px1<sup>-/-</sup> Px2<sup>-/-</sup> mice were protected in a stroke model. (A, B, D, and E) Compared with Px1<sup>+/+</sup> Px2<sup>+/+</sup> littermates, neurological deficits did not differ in Px1<sup>-/-</sup> and Px2<sup>-/-</sup> mice after MCAO as evaluated by the corner test (A and B). When measuring latency to move, Px1<sup>-/-</sup> mice showed a trend (D) and Px2<sup>-/-</sup> a significantly shorter latency than wild-type littermates (E), F(1/58) = 9.7, P < 0.01 (repeated-measures ANOVA). The dashed line indicates the expected behavior without a side preference in 12 trials of the corner test. Mice were investigated before and 24 h after MCAO. Values are mean ± SEM (n = 6-14). (G and H) Px1<sup>-/-</sup> and Px2<sup>-/-</sup> mice showed no statistically significant differences in infarct volume compared with Px1<sup>+/+</sup> Px2<sup>+/+</sup> littermates. Values are mean ± SEM (n = 15-18). (C and F) Double-knockout Px1<sup>-/-</sup> Px2<sup>-/-</sup> mice had a smaller neurological deficit 24 h after MCAO than Px1<sup>+/+</sup> Px2<sup>+/+</sup>. In the corner test the pathological preference of Px1<sup>-/-</sup> Px2<sup>-/-</sup> littermates to turn to the right was significantly reduced in Px1<sup>-/-</sup> Px2<sup>-/-</sup> mice 24 h after MCAO. F(1/12) = 6.7, P < 0.05 (repeated-measures ANOVA, n = 5-9). In the latency to move (F), Px1<sup>-/-</sup> and Px2<sup>-/-</sup> mice needed significantly less time to move compared with their Px1<sup>+/+</sup> Px2<sup>+/+</sup> littermates. F(1/12) = 5.9, P < 0.01. *P < 0.05 (repeated-measures ANOVA, n = 5-9). (I) Double deletion of both Px1 and Px2 (Px1<sup>-/-</sup> Px2<sup>-/-</sup>) significantly reduced the infarct volume compared with the Px1<sup>+/+</sup> Px2<sup>+/+</sup> littermates. **P < 0.01 (t test, n = 6–10).
health systems move quickly to stake their ground and specialist slots. Like the childhood game of musical chairs, when the music stops and decisions are made, someone may be left without a seat.

Throughout the country, neurosurgeons are feeling pressured to align with health systems or face the possibility of losing access to their patient base, new referrals, emergency coverage and even designated operating block time—all of which may be preferentially assigned to the employed or affiliated physicians.

The music already is playing. Fewer and fewer physicians practice independently, and that number is expected to continue to plunge for the next two years, according to the Medical Group Management Association and the American Medical Association. The trend is clear in neurosurgery, where employed physicians are the fastest growing practice type.

As physicians grow weary of private practice and the accompanying demands of government regulations, health plans and the onerous requirement to implement and maintain electronic medical record (EMR) systems, many seek employed positions out of frustration rather than a desire to be part of an employed physician workforce.

Independent physicians who are not affiliated with a health system face changes to traditional referral patterns in their communities, as primary care physicians and neurologists aligned with health networks are given incentives to refer to neurosurgeons within their own system. Neurosurgeons outside the network may no longer be able to see long-standing patients in their practice, and may not have access to new referrals from network-affiliated referring physicians.

Network-affiliated physicians also need to adjust to shifts in the performance measures used to establish salaries. In the Wall Street Journal article, Mathews cites the example of Dan McCullough, a family physician who works for a hospital system in Massachusetts. For McCullough, 28% of his annual pay was tied to patient satisfaction, quality and efficiency goals—a mix of his own results and those of the entire physician group affiliated with the hospital.

Neurosurgeons who join integrated health systems face similar kinds of incentive payments which may be based on patient satisfaction surveys, EMR-based performance data and other external measures that serve as surrogates to track efficiency and quality. These kinds of arrangements are designed to influence physician clinical decision-making, at least in theory to reflect evidence based best practices rather than personal or patient preference or to meet hospital targets. One of the challenges for neurosurgery is that this specialty lacks prospective and controlled studies with outcome and cost analyses to validate many practices. Comparative effectiveness research may play an important—albeit controversial—role in defining best practices for this specialty.

In the case of McCullough, making the best decision has meant angering patients who demand certain procedures—like early MRI scans for low back pain. Alternatively, health system performance incentives also reward physicians for going the extra mile to ensure that patients who abuse the emergency department get the primary care they need to prevent costly overutilization.

New cooperative deals between healthcare providers and health insurers, which are designed to both cut costs and track quality and outcomes of care, also require some adjustments on the part of the different players.

The Wall Street Journal article cites the example of health insurance giant Aetna, which has partnered with Banner Health, a 23-hospital system based in Arizona. The partnership has required the two to share information normally held close to the vest, and trust that it would not be used to unfairly benefit the other. The hospitals
have released patient information, while the insurer has disclosed how it sets its premium rates.

For physicians, data sharing will mean that interactions with patients will be carefully tracked and outcomes measured. In this scenario, even performance measures such as patient smoking interventions, for example, could be recorded and used to set neurosurgeons’ pay.

These arrangements also may change risk distribution; hospitals or physician groups may assume more of the risk—covering the costs of all care, including complications, readmissions and other consequences of challenging cases.

As distinctions in the industry are starting to blur, integrated systems may result in health insurers playing a more involved role in patient care, especially preventive care, which ultimately saves the companies money. The Wall Street Journal article cites the example of a man whose Medicare plan is owned by the health-insurance company, CareMore, which monitors his diabetes from a storefront clinic. Other insurers use electronic devices that monitor a member’s congestive heart disease symptoms using an electronic device installed in the patient’s home. Tomorrow’s integrated healthcare systems are designed so that every stakeholder has an incentive to promote healthy lifestyles and prevent chronic disease. Early evidence of integration and desire for best practices and cost-containment by physicians are the letters from insurance companies suggesting patient-care improvements, calls from discharge planners for patients with extended hospital stays, and prompts on the EMR with patient health maintenance reminders.

The desire for more healthcare dollars directed at care rather than corporate profits may eventually lead to a future in which individuals pay for membership in an integrated health system rather than pay premiums to health insurance companies. This model of care already is gaining market share in many US communities, as illustrated by the increasing success of Kaiser Permanente. In choosing to be members of integrated health systems, patients are voting with their dollars. And in a country where competition and freedom of choice is far more popular than single payer government-based healthcare, competition for members may occur among integrated health systems based on quality, service, cost, and outcomes.

The neurosurgeon’s role within the integrated health system may evolve to include support of patient education and disease prevention programs such as those that keep cholesterol and blood pressure in check to prevent stroke, as well as weight loss and conditioning programs to alleviate or prevent low back pain.

New systems of care also may reward patients for staying well with lower insurance premiums or membership costs.

Some employers already are making the controversial decision to tie employee health coverage costs to their health status. Mathews writes of MasterBrand, a unit of Fortune Brands Home & Security, which tests employees’ blood pressure, cholesterol and blood sugar, and adjusts out-of-pocket health care premiums accordingly.

This is a time of transition for the specialty. Senior neurosurgeons nearing the conclusion of their careers may choose to ride out the changes or simply retire early. Newer neurosurgeons will easily adjust, having entered the field with EMR experience and accustomed to mandated work hours and routinely recording performance measures during their residency training. The toughest adjustment may be faced by neurosurgeons in the peak of their practice, feeling forced to modify their productive and independent practice style and abandon certain career expectations in order to adapt to new healthcare models.

With cost containment at the heart of many integrated health and accountable care systems, the number of positions for specialists may be strictly limited. Once those positions are filled, theoretically it may be years before new specialists are added to a physician network.

Neurosurgeons at any stage of their career are encouraged to be smart and savvy players in the game of healthcare musical chairs, selecting necessary health system employment and alignments, or risk being left standing unaffiliated and without access to the patients they have dedicated their careers to caring for.

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### REFERENCES


### State of the Art in Subdural Grid Design: A New Flexible Active Electrode Array

Subdural recordings in patients with epilepsy play a vital role in determining the location and spreading of ictal events, and are used widely to plan surgical resection (Viventi J, Kim DH, Vigeland L, et al. Flexible, foldable, actively multiplexed, high-density electrode array for mapping brain activity in *vivo*. *Nat Neurosci.* 2011;14(12):1599-1605). Typical commercial electrodes have a fairly wide spatial pitch, on the order of 1 cm between neighboring grid contacts. Finer measurements, both spatially and temporally may eventually prove useful clinically in epilepsy surgery planning and have already provided exciting experimental results. Viventi et al have now published the results of an implantable grid system in an animal model which incorporates an array of amplified and multiplexed microsensors housed in an extremely thin and flexible substrate. They have succeeded in recording sleep spindles, single-trial visual evoked responses, and picrotoxin induced seizures in cat neocortex from this novel implantable array.

This new implantable system consists of 360 channels of active electrodes, where the electrodes are 300 μm × 300 μm, with an inter-electrode spacing of 500 μm. A total of 720 transistors were fabricated in this flexible nanomembrane, 2 transistors per electrode unit. Transfer printing technology was used for fabricating the layers which consisted of doped silicon nanomembranes, layers of metal interconnections, and insulating layers of polyimide. The array is flexible enough that it can be bent around a layer of silicone rubber to form a double-sided recording system, and the authors were able to perform interhemispheric recordings from both hemispheres in this manner (Figure). Using the multiplexed array, the sampling rate used per channel for the recordings was 277 Hz for each active electrode. The authors report that this rate can theoretically be increased to >10 kHz/sec with faster analog to digital conversion, potentially making the device useful for identifying high frequency oscillations associated with seizure onset.

Viventi et al examined their recordings while the animal was under barbiturate anesthesia. The μECoG recordings demonstrated clear sleep spindles which were highly localized spatially to areas <25 mm². This synchronous spindling...