focused on M&A in 2008–2012, indicates that—from a financial point of view—no large differences exist between the development of orphan and non-orphan drugs. Development of orphan drugs is cheaper and faster, but this benefit is offset by acquisition at a later stage. A decision to invest or start a venture in orphan drug development should—as with drugs for common diseases—be driven mainly by assessments of risk and chance of success. Here it should be noted that we have not looked at attrition rates for orphan and non-orphan drug development, as it is virtually impossible to obtain data on drug development ongoing in all privately held companies. However, attrition rates would clearly have an important impact on the return of capital invested. Another important consideration is pricing of orphan drugs—a subject of continuous debate[5,7]. Although high reimbursement prices are accepted for now, this may change in the future and could negatively impact deal terms. This may especially hold true for compounds that have limited clinical benefit or are not disease modifying.

Our analysis also reveals that despite a broad interest from big pharma in obtaining ODNs, only a limited set of players acquires rare disease–focused companies. Rare disease–focused bioentrepreneurs should therefore keep a close watch on the wish list of this limited group and seek a strategic fit[6]. To further enhance their success rate, these bioentrepreneurs should include regulatory advice and engage with the authorities as early as possible, thereby laying a clear path toward final success.

COMPETING FINANCIAL INTERESTS
The authors declare competing financial interests: details are available in the online version of the paper (doi:10.1038/nbt.2836).

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SciCafé
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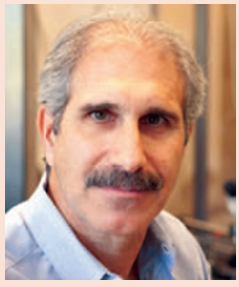
Startups on the menu

In 2009, Stanford University's Robert Malenka and Thomas Südhof gave a presentation at the San Francisco SciCafé proposing the use of short hairpin RNAs as a means to more rapidly identify the role of synaptic proteins in disease pathophysiology. Malenka pioneered the study of several proteins that alter the efficacy of neurotransmission across synapses, providing insights into the addictive effects of drugs, such as cocaine and amphetamines; Südhof's work on mechanisms for neurotransmitter release and the calcium-controlled fusion of synaptic vesicles in the presynaptic terminal was recently awarded a Nobel Prize. In 2010, Malenka and Südhof were among the cofounders of neurology startup Circuit Therapeutics, based in Menlo Park, California. Malenka talked to *Nature Biotechnology* about his experience.



Nature Biotechnology: **When did you first get involved with Circuit Therapeutics?**

Robert Malenka: I had been on the scientific advisory board for several biotechs and pharma firms over the previous 15 years and had looked at jobs in pharma, so for a while I was also considering founding my own company. One day I started brainstorming with my friend Karoly Nikolich, and it didn't take us too long to think about asking Karl Deisseroth and Tom Südhof to join. Karl had been my postdoc, and it was obvious that optogenetics had huge potential. Tom was a close scientific collaborator and was the world's leading molecular synaptic biologist—he'd just won the Nobel Prize. After some discussion, we additionally asked Scott Delp, chair of Stanford's Bioengineering Department, to join. That was our five-member founding team. We were fortunate to find a wealthy angel investor who understood our ambitious vision, and we were off and running with further support from Stanford University.

NBT: How did you identify the programs in your lab most amenable for translation?

RM: As a clinical psychiatrist and a frequent advisor to industry, I was well aware of the challenges researchers faced in trying to develop novel approaches to drug discovery for brain disorders. My own lab's work was directly relevant, since we work on circuit and synaptic mechanisms that contribute to various forms of pathological experience–dependent plasticity, which are of direct relevance to many brain disorders. In many ways this is translated through my current role at Circuit as chair of the scientific advisory board, which allows me to meet with Circuit employees fairly frequently and have many informal e-mail conversations about the science and ways to take it forward.

NBT: What lessons have you taken from your experience at Circuit?

RM: I've learned that you never stop learning and need to be very facile in thinking about what your company might do and is doing. There's never too much feedback or advice; one must solicit input from many different, experienced [venture capitalists] and entrepreneurs with different types of backgrounds. At the same time, one needs to believe in one's own vision and intuitions. In retrospect, I think Circuit could have been a bit more disciplined in its early activities and tried to do too much. On the other hand, with a recent, successful series B funding and external collaborations being seriously discussed, Circuit is in good shape with outstanding leadership. It will be very exciting to see where the company is two years from now.