To illustrate the concept of lineage reprogramming via a transient primitive state, we have developed a model based on the metaphor of a pinball machine (**Fig. 1**). In the classic model of C.H. Waddington, a cell moving toward terminal differentiation is represented as a ball rolling down along branching valleys of an epigenetic landscape. In our more interactive model, development of a cell ('ball') begins at the zygote stage and progresses through the blastocyst stage in the 'ball launch lane' (bottom right). As cells move down from the top of the panel, they differentiate into the three germ-cell lineages. A cell is driven to ectoderm, mesoderm or endoderm depending on what cues—'bumpers' or 'flippers'—it strikes. Bumpers represent endogenous transcription factors, whereas flippers represent ectopically expressed transcription factors. The latter can push the cell across epigenetic 'edges' to more primitive stages higher up on the panel or all the way to pluripotency (iPS cells) in the ball launch lane (as shown by *the* pinball wizard, Shinya Yamanaka[2,3]) as well as down specific differentiation pathways. Some master-regulator transcription factors, such as Oct4, can propel the cell a long distance toward pluripotency, whereas lineage-specific transcription factors can only tap it within a single lineage.

In the new work by Vierbuchen *et al.*[1], putative mesodermal fibroblasts were converted to an ectodermal neuronal fate with the Ascl1, Brn2 and Myt1l flippers (blue). For simplicity, we illustrate only two other examples of reprogramming: iPS cells and the intra-lineage conversion of pancreatic endocrine to exocrine cells[4].

In the future it will be of great interest to assess how this model compares to the alternative view that a cell can move laterally on the pinball machine (or through a tunnel in Waddington's model), thus converting directly to a new lineage without passing through a more primitive state. This will be a fundamental principle to understand as the field moves forward.

It will also be important to evaluate the implications of the present study for cell therapy for diseases of the brain. Intra-lineage *in vivo* fate switching within the pancreas or the ear may have immediate impact for diseases like type 1 diabetes or hearing loss. Any newly generated pancreatic beta cells or auditory hair cells would be in a suitable location. However, switching fibroblasts to neurons *in vivo* would be unrewarding as any new neurons produced would not be in their nervous system niche and would therefore be functionally ineffective. On the other hand, *in vitro*–generated neurons or neural progenitor cells may be useful in transplantation-based therapies, and the possibility of generating these cells from patient fibroblasts without going through a pluripotent stage would have the advantage of circumventing tumorigenicity concerns associated with iPS cells. For most clinical applications, however, it would be necessary to be able to expand the cells, as large numbers of cells are typically required for transplantation. Additional work is needed to determine whether the approach of Vierbuchen *et al.*[1] can be modified to produce expandable neural progenitor cells.

Whatever the future holds for this fascinating and fast-moving field, it is apparent that stem cell biologists, in the words of The Who's "Pinball Wizard", sure play a mean pinball.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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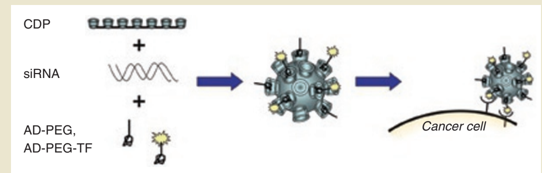
RNA interference in three humans

Many animal studies have shown the therapeutic potential of using small interfering RNAs (siRNAs) to reduce expression of target genes. Although clinical trials with siRNA are underway for a range of diseases[1], it has not yet been demonstrated that delivery of siRNA can trigger RNA interference (RNAi) in humans. For instance, in a clinical trial of intravitreal siRNA for the treatment of blinding choroidal neovascularization, the contribution of non-RNAi mechanisms to the decrease in vascularization could not be eliminated[2].

Now, Davis *et al.*[3] report in *Nature* that siRNA engages the human RNAi machinery to reduce expression of the M2 subunit of ribonucleotide reductase at both the mRNA and protein levels. The study, which is part of a phase 1 clinical trial of systemic siRNA treatment for patients with solid cancers, involved examining biopsies from just three melanoma patients who had received intravenous infusions of siRNA delivered using synthetic nanoparticles.

The nanoparticles (~70-nm diameter) were stabilized by adamantane (AD)-terminated polyethylene glycol (PEG) complexed with a cyclodextrin-based polymer (CDP). Inclusion of the human transferrin (TF) protein on the exposed ends of some of the PEG molecules targeted the nanoparticles to cancer cells expressing the TF receptor.



The authors use 5-nm gold particles to detect the nanoparticles in tumor cells, demonstrating what they believe is the first demonstration of dose-dependent accumulation of systemically delivered targeted nanoparticles in human tumors.

Characterization of the mRNA cleavage products using a modified 5′-RNA-ligand–mediated 'Rapid Amplification of cDNA Ends' method provided mechanistic evidence that the specific siRNAs engaged the RNA interference apparatus. Details of the efficacy of the approach in causing tumor regression have yet to be reported.

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