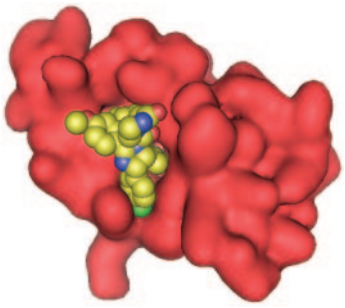
MEDICAL SCIENCES

Inducing p53 activity in tumors via nutlins

Mutations or deletions in p53 can be found in ≈50% of all malignant tumors, but activating wild-type p53 in the other 50% using small molecules is possible, report Christian Tovar *et al.* One such class of activating small molecules is the nutlins, antagonists of the p53 negative regulator MDM2. Tovar *et al.* examined the ability of nutlin-3 to restore a functional p53 pathway in tumors expressing wild-type p53. The authors randomly selected 10 tumor cell lines representing several solid tumor types, including colorectal, breast, and prostate, and examined the effect of nutlin-3 on two major p53 functions: cell-cycle arrest and apoptosis. Although nutlin-3 treatment resulted in generally uniform arrest of the cell lines in G_1 and G_2 phase, apoptotic responses were more varied. Cell lines overexpressing MDM2 showed the highest apoptotic response, whereas several others had a marginal response. Confirming the *in vitro* studies, nutlin-3 treatment also induced tumor regression in four mouse tumor xenografts. These findings support the idea that the suppressive function of p53 is preserved in many tumors, and rousing it from dormancy may be a viable therapeutic strategy in cancer treatment. — N.Z.



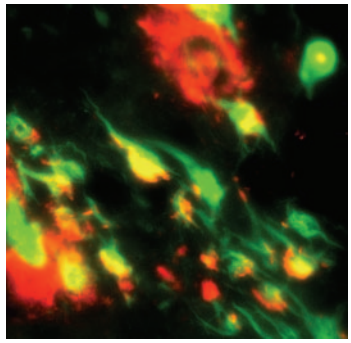
Nutlin-3 bound at p53 pocket of MDM2.

"Small-molecule MDM2 antagonists reveal aberrant p53 signaling in cancer: Implications for therapy" by Christian Tovar, James Rosinski, Zoran Filipovic, Brian Higgins, Kenneth Kolinsky, Holly Hilton, Xiaolan Zhao, Binh T. Vu, Weiguo Qing, Kathryn Packman, Ola Myklebost, David C. Heimbrook, and Lyubomir T. Vassilev (see pages 1888–1893)

NEUROSCIENCE

Beginning steps of Alzheimer's disease plaques

Jian-Ping Guo *et al.* report that soluble forms of two proteins implicated in Alzheimer's disease bind together, an event that may begin the disease process. The aggregates that cause Alzheimer's disease are insoluble clumps of amyloid-β (Aβ) protein plaques outside the cell and tau protein fibrils inside it. Guo *et al.* found that soluble, intracellular Aβ protein binds to the tau protein at early stages of the disease. Once this binding occurs, phosphorylation of the tau protein creates strong nucleation sites that cause more Aβ to aggregate inside the cell. Guo *et al.* found that the tau protein binds Aβ 1,000 times more strongly than it does to tau itself. Small soluble versions of both protein aggregates were observed inside the cells of patients with Alzheimer's disease. This early mixed protein binding may lead to the pure aggregates that disrupt neural communication and destroy neurons. Also, high concentrations of intracellular Aβ were observed by the team, as opposed to membrane-bound proteins. Guo *et al.* suggest that the strong intracellular binding of Aβ to tau may be the earliest step of the disease and that blocking this step may help prevent disease. — P.D.



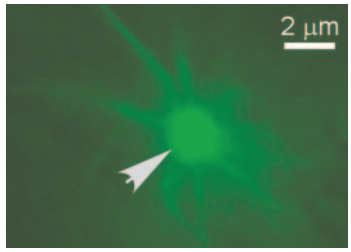
Coexpression of Aβ and tau in neurofibrillary tangles.

"Aβ and tau form soluble complexes that may promote self aggregation of both into the insoluble forms observed in Alzheimer's disease" by Jian-Ping Guo, Tetsuaki Arai, Judit Miklossy, and Patrick L. McGeer (see pages 1953–1958)

NEUROSCIENCE

Varied response of olfactory neurons to odorant

Xavier Grosmaitre *et al.* have developed a method in mice to test the electrophysiological responses of olfactory sensory neurons (OSNs) that express the same odorant receptor. Axons of OSNs that express the same odorant receptor come together into two glomeruli of the olfactory bulb. To understand the odorant response properties of OSNs expressing the same odorant receptor, Grosmaitre *et al.* used mice engineered to express the odorant receptor MOR23 together with GFP. Using perforated patch clamp recordings in intact, nondissociated mouse olfactory epithelium, the transduction currents and receptor potentials of 53 GFP^+ and 10 neighboring GFP^- cells were measured in response to lyral, a known ligand for MOR23. All GFP^+ cells responded to lyral, though the amplitude and kinetics of the response varied from cell to cell. Variations among the cells exceeded the changes for a single cell responding to different concentrations. In either voltage clamp or current clamp mode, the cells' responses increased proportionally to the concentration of odorant, with a concentration range of several orders of magnitude from threshold to saturation. An adenylyl cyclase inhibitor blocked the lyral-induced responses in the GFP^+ cells, whereas an inhibitor of the IP_3 pathway had little effect. — F.A.



MOR23 cell.

"Odorant responses of olfactory sensory neurons expressing the odorant receptor MOR23: A patch clamp analysis in gene-targeted mice" by Xavier Grosmaitre, Anne Vassalli, Peter Mombaerts, Gordon M. Shepherd, and Minghong Ma (see pages 1970–1975)