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In This Issue

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GEOLOGY, EVOLUTION

Chemical weathering shapes continents

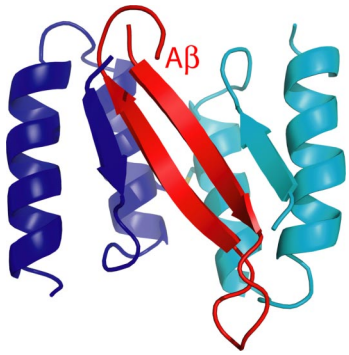
Continental crust rises higher than oceanic crust because it is less dense: It is rich in Si and poor in Mg. However, basalt, which is derived from magma, is denser and has a higher ratio of Mg to Si than the rock that makes up mature continental crust. Cin-Ty Lee *et al.* argue that chemical weathering alters the composition of continental crust as it ages and helps give it its more buoyant character. Both chemical weathering and "delamination" of Mg-rich lower crust, which occurs as it peels off and reenters the mantle, have been proposed as mechanisms that remove Mg from continents. However, quantifying the relative strength of chemical weathering versus delamination has long been a challenge. The problem is essentially that two equations arise to explain the removal of Mg, but the equations contain three unknowns and therefore cannot be solved. The authors observe that the weathering of Li and Mg is coupled, which allows the system to be solved. The authors report that chemical weathering accounts for a loss of 20% of the original basalt Mg compared with a 40% loss by other routes. From this perspective, it seems possible that life, by altering crustal chemistry via weathering, can affect the evolution of continents. — K.M.

"Regulating continent growth and composition by chemical weathering" by Cin-Ty Aeolus Lee, Douglas M. Morton, Mark G. Little, Ronald Kistler, Ulyana N. Horodyskyj, William P. Leeman, and Arnaud Agranier (see pages 4981–4986)

BIOPHYSICS

Single amyloid β-peptide examined

The aggregation of misfolded amyloid β-peptide protein into plaques is thought to be a primary cause of Alzheimer's disease. Wolfgang Hoyer *et al.* report on the detailed structure of the β-hairpin in a single misfolded Alzheimer's amyloid β-peptide. The authors bound the 40-aa isoform of the amyloid β-peptide to an engineered affinity protein and examined it with nuclear magnetic resonance spectroscopy. They found that amino acids 17–36 form the β-hairpin. The isolated hairpin strongly resembled fibrillar amyloid β-peptide. The authors found that the affinity protein stabilizes the β-sheet by extending it intermolecularly and by burying both of the mostly nonpolar faces of the amyloid β-hairpin within a large hydrophobic tunnel-like cavity. They show that the affinity protein inhibits the formation of fibrillar amyloid β-peptide. This conformation is a step toward identifying the oligomerization and fibrillation that leads to Alzheimer's disease, according to the authors. — P.D.



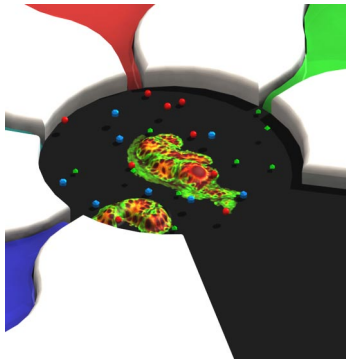
The β-hairpin of amyloid-β peptide (red), bound to an affinity protein.

"Stabilization of a β-hairpin in monomeric Alzheimer's amyloid-β peptide inhibits amyloid formation" by Wolfgang Hoyer, Caroline Grönwall, Andreas Jonsson, Stefan Ståhl, and Torleif Härd (see pages 5099–5104)

CELL BIOLOGY, ENGINEERING

Faster path to drug cocktails

A finely tuned drug cocktail is often more effective than a single drug. Finding the appropriate drug combinations in the vast realm of possibilities is much faster using a feedback control technique developed by Pak Kin Wong *et al.* In addition to the challenge posed by testing all possible drug combinations at varying doses is the need to consider their action in a biological system. To optimize combinations without requiring detailed information about individual biological pathways and interactions, the authors developed an experimental closed-loop control scheme



Closed-loop feedback control scheme.

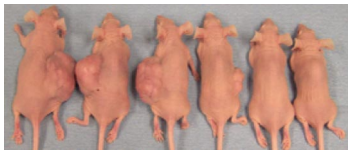
integrated with a search algorithm to identify the cocktail based on the response of the biological system as a whole. The algorithm develops its next iteration only after feedback, in this case a series of discernible phenotypic responses. The authors used the closed-loop control scheme to reduce infection of cultured cells with a mammalian virus. This approach rapidly identified a combination of drugs that inhibited almost 100% of viral activity, with lower doses of each than would be needed alone. — T.H.D.

"Closed-loop control of cellular functions using combinatory drugs guided by a stochastic search algorithm" by Pak Kin Wong, Fuqu Yu, Arash Shahangian, Genhong Cheng, Ren Sun, and Chih-Ming Ho (see pages 5105–5110)

GENETICS

MicroRNA's influence on leukemia

MicroRNAs have been predicted to influence diseases by regulating hundreds of gene transcripts at a time, but few such data sets have been identified. George Calin *et al.* present evidence that miR-15a and miR-16-1, which are known to suppress tumors through the BCL2 oncogene, activate and inactivate many genes that are implicated in human leukemia. The authors inserted the miRNAs into the genomes of tumor cells and injected them into nude mice. The miRNA clusters completely suppressed tumor growth in three of five mice and shrunk the tumors in other mice. The miRNAs also up-regulated 265 genes and down-regulated 3,307, meaning that ≈14% of the estimated number of human genes were affected. Among the many genes that were down-regulated, a significant number had AU-rich elements. An analysis of the down-regulated transcripts identified many genes that are activated in cancer by directly or indirectly affecting apoptosis and the cell cycle. The authors say that identifying the suite of silenced genes could help develop new therapies for leukemia. — P.D.



Comparison of tumor growth in nude mice.

"MiR-15a and miR-16-1 cluster functions in human leukemia" by George A. Calin, Amelia Cimmino, Muller Fabbri, Manuela Ferracin, Sylwia E. Wojcik, Masayoshi Shimizu, Cristian Taccioli, Nicola Zanesi, Ramiro Garzon, Rami I. Aqeilan, Hansjuerg Alder, Stefano Volinia, Laura Rassenti, Xiuping Liu, Chang-gong Liu, Thomas J. Kipps, Massimo Negrini, and Carlo M. Croce (see pages 5166–5171)

IMMUNOLOGY

Designer T cells prevent autoimmune disease in mice

Multiple sclerosis (MS) is an autoimmune disease that occurs when the body's T cells attack the fatty myelin sheath that insulates nerve fibers in the brain, spinal cord, and optic nerve. Without this protective layer, nerves are unable to send electrical signals and scars are formed. Joel Stern *et al*. developed regulatory T cell lines that suppress multiple autoimmune diseases in mice, including experimental autoimmune encephalomyelitis (EAE), the mouse model of MS. To create these MS-fighting T cells, Stern *et al*. immunized SJL/J mice with amino acid copolymers, then harvested T lymphocytes from the spleen and lymph nodes and used the lymphocytes to create cell lines. These new T cell lines secrete high levels of IL-10 and IL-13-immune chemicals that play an important role in immunosuppression. However, unlike traditional T cells, these lines only produce small amounts of IL-4 and virtually no TGF-β, IL-17, IL-6, IL-2, IFN-γ, or TNFα. When EAE was triggered in genetically susceptible mice, the animals developed disease at day 17 or 18. However, animals that received the IL-10-secreting T cells failed to develop EAE. The T cells also prevented the development of two other autoimmune diseases that could be induced in the same strain of mice. — B.T.

"Amino acid copolymer-specific IL-10-secreting regulatory T cells that ameliorate autoimmune diseases in mice" by Joel N. H. Stern, Derin B. Keskin, Hong Zhang, HuiJuan Lv, Zenichiro Kato, and Jack L. Strominger (see pages 5172–5176)