the small earthquakes seen in the region may arise at geometric irregularities or at secondary fractures away from the main slip zones, again a result of the complex internal structure of the fault zone[8].

A second unresolved problem is that, in the classic view, the strength of Earth's crust increases with depth in the upper to middle crust owing to the weight of the rock above, until a point between about 10 and 15 km down, where temperature comes into play. The weakening issue should therefore be most serious for the middle crust, where the predicted strength is greatest. Along the creeping part of the San Andreas, where serpentinite is known to be present at the relatively shallow depths of 3–7 km, deeper weakening processes must also be operating to fully explain the deviation of the fault from classic strength profiles. Our current knowledge of the distribution of serpentinite rocks does not, however, allow us to propose with confidence that talc is present at these deeper levels. It also indicates that other factors complement the weakening effect of talc at shallow depths.

What is more, along the central San Andreas the lack of seismicity lower down towards the middle crust — where large earthquakes on other parts of the fault often nucleate[9] — indicates that stable slip is occurring, probably through viscous deformation. This depth range is usually dominated by unstable, frictional mechanisms. In the classic view of crustal strength, viscous deformation mechanisms (such as crystal plasticity, and creep owing to the dissolution and subsequent recrystallization of rock grains under high-pressure conditions) do not operate at depths shallower than 10–15 km because temperatures above this level are insufficient.

But geological studies of exhumed former strands of the San Andreas fault system, and other similar ancient faults such as the Median Tectonic Line in Japan, show that strongly aligned phyllosilicate minerals such as micas and clays (and including talc), which are viscous at lower temperatures, replaced stronger minerals (feldspar, for example) in the fault zone at these considerable depths. This process was caused by localized metamorphic reactions encouraged by fluids within the fault zone, and is thought to explain the weak, aseismic behaviour of large faults at greater depths in the middle of the continental crust even if, as in most cases, serpentinite rocks are not present[10–12].

The overall lesson is that fluid-triggered metamorphic reactions localized in fault zones can strongly influence the strength of faults along plate boundaries and their likelihood of generating large earthquakes. Basic geological constraints such as the three-dimensional distribution of rock types and structural complexity in fault zones at relatively small scales are pivotal in the control of fault mechanics and tectonic behaviour at much larger scales. Moore and Rymer's discovery[3] is a prime example, and might not be the only gem that the SAFOD project digs up. Future collaboration between structural geologists and seismologists should yield better definitions of the composition and structure of fault zones, and their influence on the nucleation and propagation of earthquakes. ■

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BIOCHEMISTRY

Designer enzymes

Michael P. Robertson and William G. Scott

Evolution has crafted thousands of enzymes that are efficient catalysts for a plethora of reactions. Human attempts at enzyme design trail far behind, but may benefit from exploiting evolutionary tactics.

Chemical reactions in living organisms are catalysed by enzymes, the vast majority of which are proteins. These finely tuned catalysts are the result of billions of years of evolution, and far surpass anything yet created by humans. Indeed, our ability to design enzymes, on the basis of our knowledge of protein structure and reaction mechanisms, can most charitably be described as primitive. The structure and catalytic properties of an enzyme are dictated by its amino-acid sequence in ways that are not understood well enough to reproduce. On page 828 of this issue, Seelig and Szostak[1] describe how they bypass this intractable difficulty by simulating evolution. They use an *in vitro* artificial selection process to isolate new protein enzymes that join the ends of two RNA molecules together.

The ability to make enzymes for specific purposes is of great practical interest — designer enzymes could be made for many potential applications. They could, for example, be used to prepare drugs efficiently. In fact, some methods for preparing new enzymes already exist. One approach is the randomization and *in vivo* selection of variants of existing enzymes. This strategy has been reasonably successful, but it is limited by the relatively small number of possible variants (typically from 10^6 to 10^8; for comparison, a system that generates more than 10^{12} would be desirable).

Another approach is to use an organism's immune system in a form of natural selection to create catalytic antibodies[2,3]. Enzymes work by binding and stabilizing the transition state of a reaction — the highest-energy configuration of atoms in the reaction pathway. So if an antibody can bind to molecules that have the same geometry as a reaction's transition state, then it can also catalyse that reaction. Generating catalytic

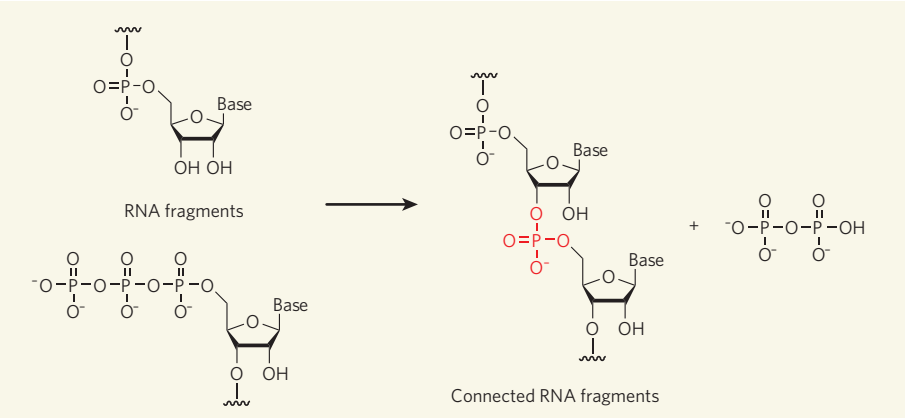

Figure 1 | Artificial enzyme evolution. Seelig and Szostak[1] have developed an *in vitro* method for evolving protein enzymes that can catalyse bond-formation reactions. Using this method, they generated an RNA ligase enzyme that forms a phosphodiester connection (red) between two RNA fragments.

antibodies thus requires a detailed knowledge of the reaction's mechanism and the ability to synthesize a transition-state mimic — conditions that are often not met.

Catalytic antibodies can be thought of as rationally designed enzymes, because knowledge of the reaction pathway is required to make them. But the creation of particular antibodies in this way is purely the product of *in vivo* genetic rearrangements that generate a vast number of antibody variants, and of the immune selection process itself. Catalytic antibodies typically provide a 10^4-fold to 10^6-fold rate enhancement of reactions, but usually fall short of the catalytic prowess exhibited by their natural enzyme counterparts. This is probably because transition-state stabilization is only one of several strategies used by natural enzymes to accelerate reactions.

By contrast, enzymes have evolved naturally in a selection process that deals directly with reactants and products, but only indirectly with transition states. Seelig and Szostak[1] use this natural strategy to discover enzymes that catalyse bond-forming reactions. They use a technique known as mRNA display, in which proteins to be screened for catalytic activity are each tethered to the specific messenger RNA (mRNA) that encodes that protein (see Fig. 1a on page 828). Complementary DNA (cDNA) is generated from the mRNA, using a primer that has a substrate attached, thus creating an mRNA–cDNA duplex with a protein and substrate attached. The authors then add a second substrate that incorporates an anchor that can be immobilized. If the protein catalyses a bond-formation reaction between the two substrates, then it will be immobilized — and thus selected — through the anchor. The authors amplify selected cDNA that corresponds to an active enzyme, and use this to encode proteins for a subsequent round of selection. By generating random mutations in the cDNA before amplification, the authors create an artificial evolution process that optimizes enzymes for the catalytic activity over several rounds of selection.

Seelig and Szostak's technique[1] has the practical advantage that the entire process is carried out *in vitro* with a large set of proteins — their study uses 10^{12} unique sequences. The authors used their method to isolate RNA ligase enzymes, which catalyse the formation of a bond between two pieces of RNA (Fig. 1). Previously reported mRNA-display selections[4] were limited to isolating proteins that simply bind to target molecules. Seelig and Szostak have achieved a significant breakthrough by using mRNA display to evolve proteins that not only bind to target molecules, but also catalyse enzymatic reactions that use the bound target molecules as substrates.

Although proteins have won the fitness contest of natural selection to become the pre-eminent enzymes, billions of years ago life may have started with RNA enzymes — ribozymes — in a putative RNA world that pre-dated proteins and DNA. The RNA bond-forming (ligation) reaction is a favourite of those studying evolution from an RNA world, because it is presumed to be the crucial chemical step of RNA self-replication[5]. Szostak and fellow molecular biologist David Bartel were the first to isolate a ribozyme ligase[6], using artifical selection. Their technique is the prototypical method for the *in vitro* evolution of ribozymes, and has been adapted for protein enzymes by Seelig and Szostak in the current study[1].

The authors' protein-based ligases don't make better enzymes than their RNA equivalents, which may seem surprising, given that evolution apparently replaced ribozymes with protein enzymes. So how can this observation be explained? It is possible that some of the catalytic potential of proteins goes untapped by artificial selections that are based only on product formation. mRNA-based selections deal most directly with enzyme–product interactions, whereas earlier catalytic-antibody selections mainly involved interactions between enzymes and transition states. The two methods could potentially select for different aspects of enzyme catalysis, and so provide complementary glimpses of the processes that governed the evolution of naturally occurring enzymes. Perhaps protein enzymes are better catalysts in part because they have a greater propensity to form transition-state-stabilizing interactions. Designing a selection process that includes ground-state interactions (as Seelig and Szostak's study[1] does) and transition-state interactions (as the previous catalytic-antibody approaches did) might yield even better-designed enzymes. ■

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MATERIALS SCIENCE

Metal turned to glass

Gilles Tarjus

In order to form a glass by cooling a liquid, the normal process of solid crystallization must be bypassed. Achieving that for a pure metal had seemed impossible — until pressure was applied to liquid germanium.

Glasses are nothing but frozen liquids: closely packed, but randomly ordered assemblages of molecules that no longer flow on any reasonable timescale (by human standards), and thus are solids for all practical purposes. Being a solid while lacking the long-range order typical of that phase of matter is what gives glasses the physical properties that make them so useful in our everyday life. On page 787 of this issue, Bhat *et al.*[1] add another member to this ubiquitous family of materials: a glass made by cooling a pure, 'monatomic' metal.

Glasses can be formed from a great variety of materials, irrespective of the type of interaction prevalent among their constituent atoms or molecules — whether covalent, ionic, hydrogen, van der Waals or metallic bonds. Most commonly, glasses are made by cooling a liquid, with the prerequisite that crystallization into a regular solid does not occur first along the way. More than 50 years ago, David Turnbull discovered[2,3] that molten metals can be cooled to below their melting point and retain their liquid structure, a phenomenon described as supercooling, or undercooling. But the tendency of such systems to crystallize is very strong, and metallic glasses have so far been obtained only by mixing several cleverly chosen components into an alloy.

Why would finding a one-component metallic glass be so important? It is probably less notable in terms of direct technological applications than for the progress it could generate in our understanding of glass formation. To quote Turnbull[4]: "The most convincing evidence of the universality of the glass state would be the demonstration that pure monatomic substances...can be put into the glass form." One might add that these substances should be characterized by simple inter-atomic forces that do not involve strong directional bonding: liquid selenium, for instance, is a non-metal in which the atoms form covalently bonded, polymer-like chains, and is easily vitrified.

A central issue is to determine the factors that allow crystallization to be bypassed as a substance is cooled past its melting point. It has been known for decades that the rate at which the liquid is cooled must be fast compared with the time taken for crystals to form. The trick is to find ways of slowing the crystallization down. In the case of metallic materials, widely applicable empirical rules have been devised by which the thermodynamic propensity towards crystallization is repressed, and the temperature of crystal formation is reduced. The effect is that atomic motion at the point of