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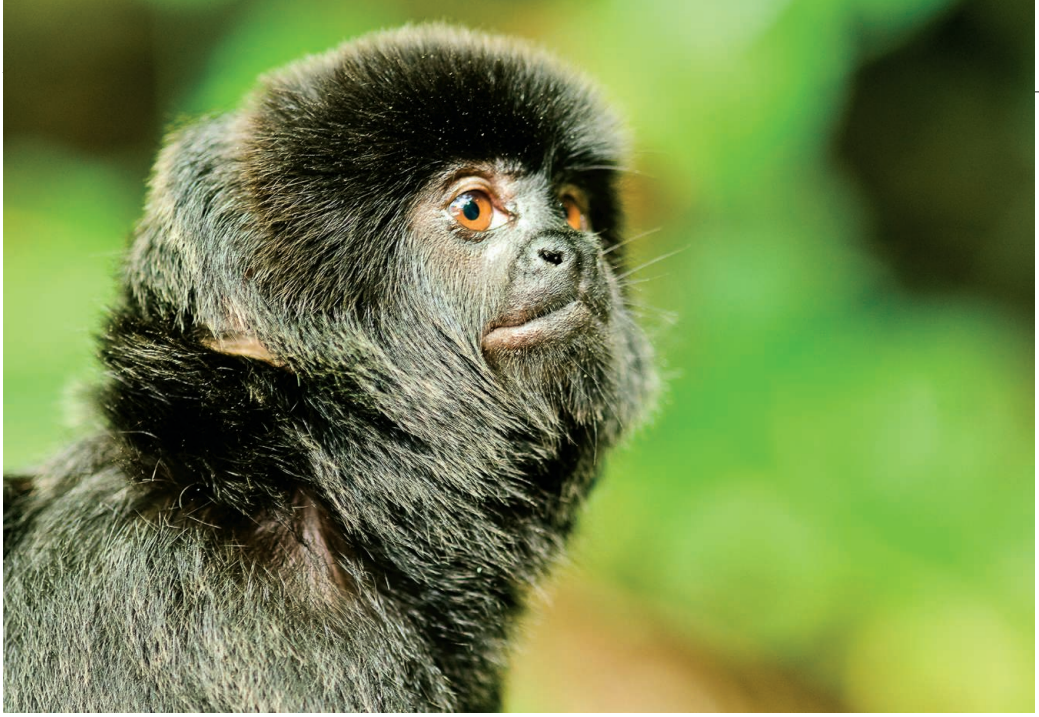

Callimico goeldii, a South American New World monkey.

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ANTHROPOLOGY

New World monkey origins

Fossils in Peru raise questions about the early evolution of monkeys in South America

By **Richard F. Kay**

New World monkeys (Platyrrhini) appeared suddenly in South America in the middle Cenozoic. Little is certain about their origin, but theories include an African source, either by vicariance through Cretaceous rifting of South America from Africa, or an Atlantic Ocean raft crossing in the middle Cenozoic. A recent fossil discovery in Amazonian Peru reported by Bond *et al.* (*1*) has identified the oldest platyrrhine primate (named *Perupithecus*) at 36 million years ago (Ma), with features that suggest links to African anthropoids of similar age. Although the new fossils reinforce the African rafting source, the details of the author's origin scenario will be controversial.

The new specimens (three cheek teeth) come from Santa Rosa in Amazonian Peru and are claimed to be approximately 10 million years older than the hitherto oldest Neotropical record of monkeys, represented by ~26-Ma Bolivian *Branisella* (*2*, *3*). The greater antiquity of Platyrrhini is consistent with molecular clock phylogenies that place the time of a cross-Atlantic monkey emigration (with their rodent fellow rafters) at 40 to 44 Ma (*4*, *5*). The new fossils also are concordant with 37-Ma African fossils that belong to the catarrhine anthropoids (Old World monkeys, apes, and humans) establishing that the catarrhine-platyrrhine split had already occurred (*6*).

That *Perupithecus* is the oldest known stem platyrrhine is highly probable. The new specimens leave no doubt that platyrrhines came from Africa, and *Perupithecus* begins to span the missing 11-million-year platyrrhine lineage (from the 37-Ma catarrhine to 26-Ma *Branisella*).

Without a radiometric age, the dating of Santa Rosa is based on rodent biostratigraphy. Increases in body size and tooth crown height are common in rodent lineages. The lower tooth crowns of Santa Rosa rodents compared with those at Salla suggest that Santa Rosa is older than Salla (*7*). Two Santa Rosa rodent species also occur in another Amazonian Peruvian fauna at Contamana, with an estimated age of 41 Ma (*8*). The Santa Rosa rodents are larger than their congeners at Contamana, suggesting a younger age for Santa Rosa. Thus, though imprecise, the age of Santa Rosa is likely between 29 Ma (the age of the oldest Salla rodents) and 41-Ma Contamana (*9*).

The teeth of the Santa Rosa monkey are more primitive than those of any known platyrrhine, supporting Bond *et al.*'s view that *Perupithecus* was a stem platyrrhine.

More controversially, Bond *et al.* suggest that *Perupithecus* is nested within a Late Eocene (38 to 34 Ma) African anthropoid group composed of *Catopithecus*, *Proteopithecus*, and *Talahpithecus*. The details of this new phylogenetic proposal are inconsistent with what we known about early anthropoid evolution (fig. S1). Three distinct anthropoid clades were present in the African Late Eocene (Afrotarsiidae, Parapithecoidea, and Oligopithecidae). Each occupied a disparate position on the anthropoid evolutionary tree and represents several immigration events from Asia (*6*). Bond *et al.* propose a very different tree of early anthropoid evolution. Solely using dental characters in their phylogenetic analysis, they join *Perupithecus* with stem taxa of two of the African clades: *Proteopithecus* is a parapithecoid and *Catopithecus* and *Talahpithecus* are oligopithecids. Bond *et al.* place these four genera together, forming an African stem platyrrhine cluster. If correct, New World monkeys would have had an African radiation before reaching South America. This radial reordering of early African anthropoids likely will be viewed skeptically by most paleoanthropologists, who will regard it as a polyphyletic pastiche requiring better supporting evidence to be considered a plausible scenario.

A key test of Bond *et al.*'s phylogenetic conclusions will be an expanded analysis beyond dental data, adding informative characters of cranial and postcranial anatomy which, although unknown in *Perupithecus,* would greatly alter the underlying tree topology. *Perupithecus* is similar dentally to Eocene African anthropoids, but cranial and postcranial evidence to date rejects a sister-group relationship of *Proteopithecus* and *Catopithecus*; *Proteopithecus* shares postcranial specializations with parapithecids. *Catopithecus* has the derived dental and postcranial characters of oligopitecids and perhaps catarrhines (*10*). Poorly known, *Talahpithecus* is possibly another oligopithecid.

Another test is to examine the degree to which the phylogenetic analysis of Bond *et al.* agrees with well-corroborated extant New World monkey phylogenies that are based on genomic sequences. Bond *et al.* include 15 of the 16 living platyrrhine genera for which there is a robust genetic tree (*11*). Their parsimony analysis of dental data

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differs greatly from the genetically based tree of extant species; it does not recover the extant platyrrhine family Cebidae and misplaces many extant genera within their respective families.

Although platyrrhines almost certainly rafted from Africa in the mid-Cenozoic, a precise link between Amazonian *Perupithecus* and any particular African taxon or taxa remains obscure. The fragmentary nature of the new fossils, the use of a morphological data set with only dental characters, and conflicts with genetic data raise doubt about Bond *et al.*'s conclusions. Their tree may minimize convergent evolution (homoplasy) in the dentition, but it omits cranial and postcranial characters for which their proposed topology would increase homoplasy. Likewise, gene sequence data must provide a framework for the placement of extinct taxa when analyzed in combination with living ones.

Perupithecus reveals tantalizing information that the niche of the earliest platyrrhines was very different from that of its larger, more herbivorous living relatives. Its small body size and molar structure suggest insectivory (*12*). Coexistence with brachydont rodents suggests that it was a forest dweller much like Late Eocene African anthropoids. This pattern contrasts with the adaptations of the younger *Branisella*—a larger, more frugivorous, and possibly scansorial (climbing) animal (*13*). *Perupithecus'* presence in today's Amazon basin confirms that this region was long the center of platyrrhine development that still is largely unknown (*14*). ■

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SUPPLEMENTARY MATERIALS

www.sciencemag.org/content/347/6226/1068/suppl/DC1
Fig. S1

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RNA INTERFERENCE

Drugging RNAi

RNAi therapeutics are emerging as a major drug discovery engine

By **Dirk Haussecker**[1] *and* **Mark A. Kay**[2]

RNA interference (RNAi)–based drugs harness endogenous posttranscriptional gene silencing pathways for therapeutic purposes. The goal is to turn down or shut off the expression of genes known to contribute to or cause disease. RNAi "triggers" are typically double-stranded RNAs (dsRNAs) of which one strand has a sequence complementary to that of a messenger RNA (mRNA), resulting in the reduction or elimination of that an mRNA and its corresponding protein product. The dsRNAs can be provided as synthetic oligonucleotides or as genetic DNA templates from which the RNAi triggers are transcribed in the target cells (vector-based transcriptional RNAi) (see the figure).

Key to the therapeutic utility of these RNAi triggers is the ability to introduce them into their target cells in the body. Such delivery is typically facilitated by formulation into nanoparticles, simple conjugates, or viral vectors (see the figure). To date, at least three delivery technologies (liposomal nanoparticles, simple conjugates, and polyconjugates) have shown highly persistent silencing of target gene expession in the liver of humans and nonhuman primates, suggesting therapeutic dosing frequencies as low as once-monthly or once-quarterly (*1*–*3*).

There are two lead RNAi drug candidates (ALN-TTR02 and ALN-TTRsc) in phase III trials that target the disease-causing mutant *transthyretin* (TTR) mRNA in the liver for the treatment of familial amyloid polyneuropathy. Given that deficiency of the TTR gene product is expected to be well tolerated and the mutant TTR protein causes the disease, the target risk is low, and commercialization may happen as early as 2017 (ALN-TTR02). Beyond the TTR amyloidosis candidates, there is an expanding pipeline of RNAi gene targets in the liver. These include candidates for diseases ranging from important public health issues (e.g., hepatitis B virus infection, common forms of metabolic and cardiovascular disorders, liver cancer) to the rare and severe (e.g., triglyceride-related pancreatitis, primary hyperoxaluria 1, α_1-antitrypsin–related liver disease). *N*-Acetyl-galactosamine (GalNAc) siRNA conjugates targeting the liver have emerged as an attractive delivery option offering the prospect of infrequent (once-monthly or even once-quarterly) subcutaneous dosing, making them suitable for other common chronic diseases such as type II diabetes and hypercholesterolemia (*2*).

Although the liver is a favored organ for delivery owing to its physiological role in removing particles from circulation, it is less clear whether new approaches aimed at nonhepatic tissues will provide therapeutic efficacy. These smaller nanoparticles, conjugates, self-delivering RNAi triggers, cationic lipoplexes, and transcriptional RNAi methods hold particular promise for targeting cancer cells, phagocytic cells, vascular endothelial cells, cell populations in the kidney, cells in the back of the eye, and the various cells types in the central nervous system (CNS) (*4*).

For diseases requiring life-long treatment, as well as for the hard-to-reach (e.g., CNS) tissues and/or tissues that rapidly turn over, such as blood-derived stem cells, transcriptional RNAi methods currently have a practical advantage, because of the prospect of persistent activity after single administration. In addition, transcriptional RNAi may be a better match for certain diseases where both the addition of a normal gene, as well as silencing of the endogenous mutated gene, are beneficial. This would include diseases such as sickle cell anemia (*5*) or the most common form of α_1-antitrypsin deficiency (*6*). However, one disadvantage is that dosing is more difficult to control with vector-transcribed RNAi. Transcriptional RNAi candidates in clinical development today address cancer, HIV, and hepatitis C virus, as candidates for α_1-antitrypsin deficiency and neurodegenerative disorders approach the clinic. This compares to over 20 synthetic RNAi trigger clinical candidates.

> ***"Beyond the TTR amyloidosis candidates, there is an expanding pipeline of RNAi gene targets..."***

It remains to be seen how the safety profile from the largely short-term experience

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Supplementary Materials for

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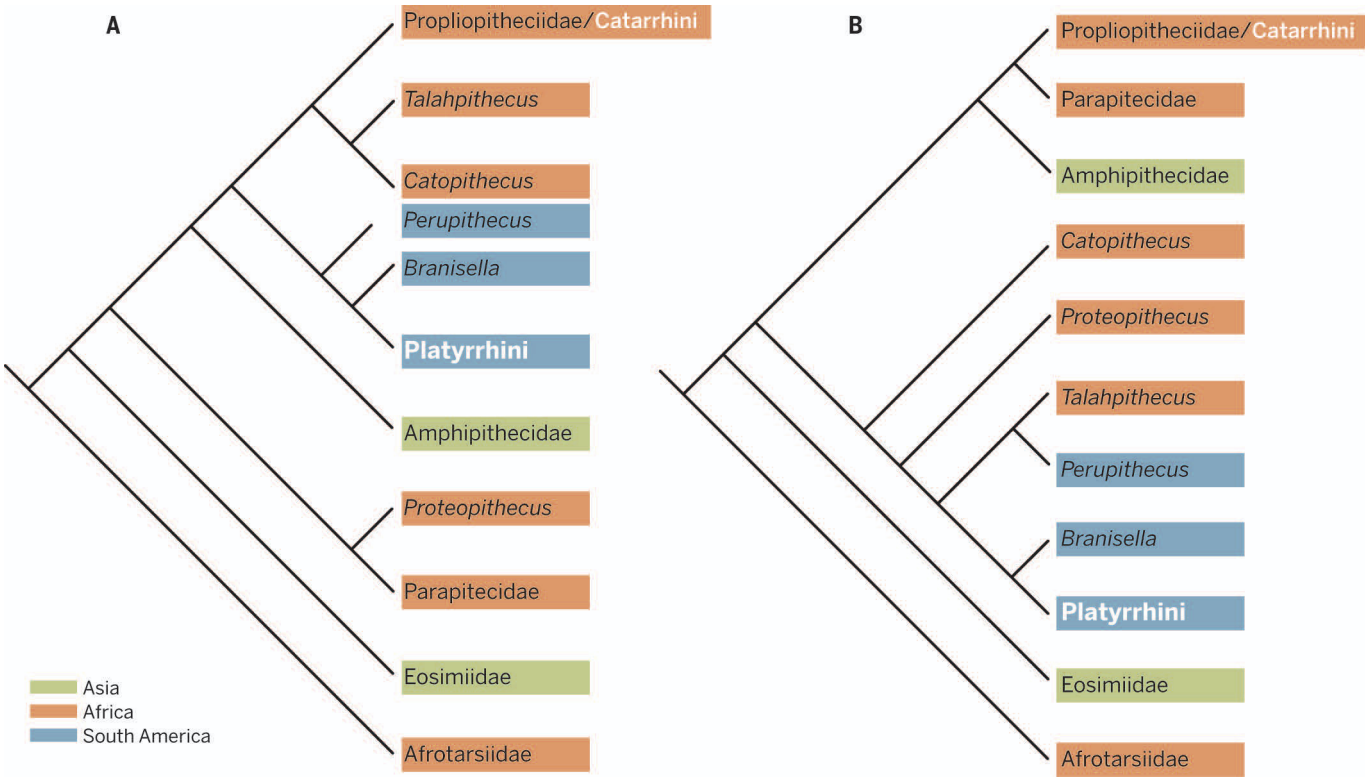

Fig. S1. Contrasting view of early anthropoid evolution. (**A**) Summary phylogeny of (*6*) is shown with probable position of *Perupithecus* indicated. (**B**) New views (*1*) challenge the previously proposed phylogenetic tree.

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