challenging because of its small size, short length, high flexibility, and structural instability; many investigators questioned whether RNP has a well-defined helical symmetry.

The two research groups accomplished this seemingly impossible task with the iterative helical real-space reconstruction method (6), in which the central helical region was divided into small fragments and initial helical parameters were determined from non-averaged maps. The two termini of the RNP were separately extracted and reconstructed. As a result, the RNP structures reported in both papers are montages assembled from three independent reconstructions. Variations are noted in the helical parameters and the NP orientations of the two RNP models reported by the two groups. Possible explanations for intermodel variations include the model resolution, different handedness of the electron density maps, rotational freedom of the NP molecules, and source of RNP samples (viral particles versus cells).

The work by Arranz et al. and Moeller et al. greatly expands our horizon by establishing reliable methods for the isolation and structural characterization of the influenza virus RNP. Further studies of this kind would allow scientists to address many long-standing questions in the flu field. For instance, how does the helical structure of RNP rearrange during viral RNA transcription and replication? When do newly synthesized RNPs adopt the double-helical morphology? And how do the eight RNPs of influenza A interact with each other to mediate genome packaging and gene reassortment? Novel biochemical approaches combined with ever-improving computational and structural techniques should help to uncover much-needed insights into these complex yet intriguing problems.

References and Notes

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HISTORY OF SCIENCE

Tackling Meningitis in Africa

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The United States is currently in the midst of a meningitis outbreak (with at least 36 deaths) as the result of fungal contamination of steroid injections to relieve back pain (1). In Africa’s so-called “meningitis belt,” outbreaks of meningitis are a regular occurrence, killing thousands and infecting tens of thousands each year. In 2009, about 5300 people died of meningitis and 88,000 were infected with the disease (2). The meningitis belt stretches from Senegal in the West to Ethiopia in the East and includes around 300 million people. Sanofi Pasteur had provided Africa with a meningitis vaccine for decades but because of reduced supplies in 2006 and 2007, and a threat of increased incidences of the disease, the World Health Organization (WHO) made a call for additional vaccine providers (3). But it wasn’t multinational companies from wealthy nations that responded, but two Latin American countries that answered the call. What brought Brazil and Cuba together in this seemingly unlikely collaboration?

It was the entrepreneurial arms of two public research organizations in Brazil and Cuba—Bio-Manguinhos and the Finlay Institute, respectively—that jointly proposed to manufacture a polysaccharide vaccine against meningitis (serotypes A and C).

In recognizing that this partnership could indeed meet the demand, the WHO supported the alliance and prequalified their vaccine. The venture has since supplied more than 19 million doses (4), distributed through the WHO, United Nations Fund for Children (UNICEF), Doctors Without Borders, and the International Red Cross, among other organizations.

This apparently straightforward account of how two enterprises came together to provide a much needed treatment is based on a relationship that developed over time. The ability of both countries to produce vaccines had been built over decades (5–8). Cuba, with a relatively strong record of innovation, had created a synthetic vaccine against Haemophilus influenzae type b (Hib) and a meningitis BC vaccine (9); its expertise was key to providing the active ingredients of the meningitis AC vaccine. Vaccine production was the strength of Bio Manguinhos; its use of lyophilization (freeze-drying) improved vaccine stability, storage, and transport. By harnessing their respective capabilities, Bio-Manguinhos and the Finlay Institute could together respond fast and effectively to the meningitis outbreak. Although neither country had suffered serotype A meningitis, they could respond to an outbreak elsewhere.

The production capacities of Bio-Manguinhos and the Finlay Institute also allowed them to provide a relatively inexpensive meningitis vaccine. Their price was US$ 0.95 a dose compared to $15 to $20 a dose for polysaccharide vaccines against serogroups AC, W135, and Y on the international market, and $80 a dose for a conjugated meningitis vaccine used in high-income countries (4, 10) (the latter type provides broader protection and a longer immunization period). Because the Brazil-Cuba vaccine targeted the meningitis strain in Africa, the two organizations had to develop an inexpensive health product accessible to the local populations.

Another reason for the success of the Brazil-Cuba venture

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How did two Latin American countries harness their scientific strengths to address a major medical problem in Africa?
was their prior work together in the biopharmaceutical sector. Since the late 1990s, the governments of Brazil and Cuba had been steadily promoting scientific interaction to emphasize South-South collaboration. This sector was singled out for partnerships given each nation’s strengths in this arena as well as some common health problems such as tropical diseases and a growing noncommunicable disease burden (including cardiovascular disease and cancer). Together, they had an applied focus—to increase the availability of affordable health products that serve local health needs. Bio-Manguinhos had already collaborated with several Cuban biotechnology institutes and, for example, transferred affordable technologies from Cuba to produce interferon alpha-2b and erythropoietin. The main benefits of these joint projects were savings for Brazil’s public health system and income from royalties for Cuba. These earlier, mutually beneficial collaborations were a strong foundation to build upon.

The Brazil-Cuba meningitis project was not their only collaboration to have benefited a third party. They are now jointly promoting health and development in Haiti following the 2010 earthquake and will construct hospitals, support immunization programs, and strengthen laboratories for disease surveillance in Haiti (11).

Most international collaborations include elements of self-interest and desires for the alliance to benefit all parties concerned. Sometimes developing countries are transparent about this and “tie” their aid by demanding that products and services be supplied exclusively by them instead of being purchased on the international market. China and India, for example, tie their aid to Africa by requesting that services and products in their African initiatives be supplied by them (12, 13). However, South-South and North-South approaches to assistance can be viewed as having different philosophies. Whereas the latter is generally grounded in altruism, the former is built on solidarity between countries that have had to survive under challenging conditions. This distinction sets a different tone for South-South collaboration. The solidarity among developing countries began to surface in the 1950s during the quest for independence from colonial powers, and many developing nations sought alternatives to dealing with the North to address issues of concern. Today, there is an increasing scope for South-South interaction, as the developing world becomes technologically proficient and experiences economic growth (14). South-South partnerships are therefore promising for tackling many shared challenges in health, agriculture, and environmental protection. Given that aid from traditional Northern donors is declining with the continuing global economic recession (15), international and philanthropic organizations, and governments in high-income countries, should recognize South-South enterprises to a larger extent in strategies that promote global health and development.

References and Notes
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EVOLUTION

Splicing in 4D

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Flexibility in regulating RNA splicing can generate diverse phenotypic differences among equivalent organs across vertebrates.

In the chapter of The Origin of Species entitled “Difficulties on Theory,” Charles Darwin found it “most difficult to conjecture by what transitions an organ could have arrived at its present state.” On pages 1587 and 1593 of this issue, Barbosa-Morais et al. (1) and Merkin et al. (2) advance our understanding of the molecular mechanism by which the genome generates differences in organs between species. This part of the answer relies on the broken syntax of genomic messages and uncovers striking differences in how evolution shapes the different layers of gene regulation.

Genes in eukaryotic organisms are first transcribed as precursor messenger RNAs (pre-mRNAs) in which “meaningful” sequences (exons), which code for amino acids or harbor regulatory sequences, are interrupted by (usually) longer pieces (introns) that are removed by splicing. The resulting mature mRNAs are then translated into proteins, which carry out enzymatic and structural functions in the cell. Remarkably, different cell types can interpret the same sequence of a pre-mRNA either as an exon or as an intron. This leads to different patterns of splicing that represent cell type–specific alternative interpretations of the genomic information. Alternative splicing allows the shuffling of protein-coding domains or confers distinct sensitivity of the spliced mRNAs to regulatory factors (3). Thus, gene transcription and alternative splicing provide separate mechanisms by which particular cell types can determine the complement of proteins required for carrying out their specialized functions in the organism.

Patterns of tissue-specific gene activation are highly conserved among vertebrates. Indeed, Merkin et al. find that only when considering long evolutionary periods (e.g., 300 million years after the split between birds and mammals) can a species-specific signa-