spins and ^{71}Ga nuclear spins in these semiconductors, the magnetization of the conduction electrons yields an effective magnetic field H_{eff} acting on the nuclear spins in contact with the electron gas. In particular, if the nuclear spins are polarized by an external field $H_{ext} \| H_{eff}$ and subsequently tipped to lie in a direction perpendicular to H_{ext} and H_{eff}, nuclei in contact with the electron gas will precess at a rate proportional to $H_{ext} + H_{eff}$, emitting radio frequency radiation with a spectral content that can be measured. Because the nuclei in the rest of the sample will only feel the external field, a shift in frequency may be observed between the two groups of nuclear spins. This "Knight shift" is then a measure of the electron gas spin polarization.

If all the ^{71}Ga nuclei in the sample precess, then those contributing to the Knight shift are obscured because their relative abundance is small. However, Kuzma *et al.* used an optical technique to selectively polarize nuclei in the vicinity of the electron gas, thereby minimizing this background, permitting detailed studies of the the electron spin polarization (see figure).

Because the optically induced nuclear spin polarization diffuses away from the region of the electron gas somewhat before the tipping pulse, the spectral content of the spin precession shows a residual contribution from the barrier region of the host semiconductor. This signal's frequency is then used as a reference from which the Knight shift can be accurately measured. The data of Kuzma *et al.* demonstrate that the spin polarization of the electron gas decreases as the system is tuned away from $\nu = 1/3$, revealing the presence of spin-reversal charged excitations. Moreover, rather than observing an individual, shifted frequency, a distribution of Knight shifts is obtained that results from the spatial inhomogeneity of the electron gas magnetization. Although broadening can be expected simply from the variation in the gas density along its confinement axis, the authors observe an additional linewidth accompanying the reduced polarization that suggests the localization of these spin-reversed excitations in the plane of the electron gas layer. Surprisingly, they find that this spatial inhomogeneity of the spin polarization is maintained over a 40-μs time scale, which is extraordinarily long for a 2D electron system.

These findings suggest a remarkable decoupling between the energy of the two-dimensional electron gas spins and their environment. As discussed above, this is an important first ingredient in the fabrication of spin-polarized solid-state devices and is characterized by the longitudinal relaxation time, or $T_1 > 100$ μs, of the electron gas magnetization. A second important quality is the ability to manipulate the spin system, and Kuzma *et al.* have also shown that radio frequency radiation couples to these spin excitations. This suggests the exciting possibility that resonance techniques conventionally targeted at nuclear spins may ultimately prevail in controlling these electronic spins as well.

Because these spin excitations appear thermally insulated, the coherence of the spin system may also be similarly isolated, as the exchange of energy between the spins and a heat bath puts a limit on their coherence time. For noninteracting electron spins, the transverse spin relaxation time T_2 characterizes the intraspin quantum coherence time and may be measured by preparing an ensemble of such spins in a superposition of their energy-split basis states and studying the resulting spin precession. Within a collection of interacting spins, the issue of single-spin coherence is more difficult to resolve by such means; however, recent optical experiments have shown that environmental contributions to electronic spin decoherence in semiconductors can be dramatically reduced by the removal of magnetic impurities and the introduction of electrical dopants. With Kerr and Faraday rotation studies of electron spin precession, T_2 values of greater than 100 ns have been reported in Si-doped bulk GaAs (*4*). These phenomena are so robust that spin precession in electron gases endures for nanoseconds even at room temperature (*5*). An important common feature shared by these experiments and those of Kuzma *et al.* is that a sea of electrons enables long-lived spin phenomena. For collective spin excitations (*2*), the issue of coherence remains an open question. Spin precession measurements are appropriate for simple spin systems represented by a basis of Zeeman split levels because the coherent evolution of such a system results in classical precession. However, for collective modes, more subtle tests of coherence are probably necessary and can only be devised when the spectrum of these modes is better understood.

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MEETING THERAPEUTICS

Genetic Medicine—When Will It Come to the Drugstore?

Pernilla Wittung-Stafshede

The latest discoveries in the field of genetic drugs—molecules that directly target the nucleic acids DNA and RNA—were discussed at the recent Nobel workshop "Gene-Targeted Drugs: Function and Delivery" held in Stockholm, Sweden (*1*).

The appealing feature of the widespread "antisense" approach to genetic drug design, in which a single-stranded oligonucleotide DNA analog binds to and inhibits the RNA copy of a gene, is the apparent chemical simplicity of the molecular recognition: Formation of the antisense DNA–RNA hybrid is based on well-understood Watson-Crick base-pairing. In spite of the apparent transparency of the mechanism, however, oligonucleotides—typically 15 nucleotides long—are large molecules and are difficult to deliver to the insides of cells. Another class of antisense molecules, the phosphorothioates, have a sulfur in the oligonucleotide backbone instead of an oxygen atom and are the most promising DNA analogs so far. Currently six such antisense agents from ISIS Pharmaceuticals are in human clinical trials for use in the treatment of cancer and HIV, and as anti-inflammatory agents. M. Manoharan (ISIS) reported their recent efforts at tuning the pharmacokinetic and pharmacodynamic properties of their potential drugs by combining several modifications of the oligonucleotides. For example, modification at the 2′-position of the sugar by creating methoxyethyl, aminopropyl, and fluorine conjugates has dramatic effects on stability and target-binding efficiency. The complexity of these drug molecules' actual behavior in living systems was discussed by S. Agrawal (Hybridon Inc.). Nonspecific effects due to their association with proteins and to the base sequence of the oligonucleotide can limit or even alter the expected antisense effects. The problem of poor uptake into cells was addressed by C. Stein (Columbia University), who discussed novel delivery vehicles based on

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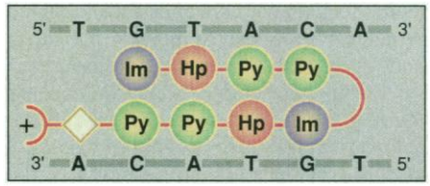
cationic porphyrins, which improve oligonucleotide cell penetration.

Another class of compounds, the PNAs (peptide nucleic acids), is quite different in that it has a peptide-like backbone instead of the normal sugar and phosphate groups of DNA. One of the inventors of PNA, P. Nielsen (Copenhagen University), showed that PNA could enter bacterial cells and kill them. This may be an important finding since increasing numbers of bacterial strains become resistant to antibiotics and alternative treatments are needed. He speculated that PNA may also be used to turn on specific genes by binding to a promoter region of a gene to initiate RNA transcription. E. Uhlmann (Hoechst) tries to combine the best of both worlds by making chimeric molecules of PNA and DNA. The DNA portion will allow enzymes attacking DNA-RNA hybrids to cut the RNA part of the complex into pieces (leading to dissociation of the drug molecule, which can then be reused), whereas the PNA portion will contribute stability and selectivity.

Genetic drugs can also be directed at the gene itself. The code for targeting the RNA copy (single stranded) of a gene was outlined almost 50 years ago by Watson and Crick. The DNA of the gene is double-stranded, and here the molecular recognition problem is not as straightforward. Since there is only one copy of many genes in a cell, this "antigene" approach is, however, a very attractive one.

The first chemical approach to target double-stranded DNA has been to use oligonucleotides to bind in the major groove of DNA and form a specific local triple helix. C. Helene (Museum National d'Historie Naturelle) demonstrated successful tests of blocking transcription of the HIV genes *nef* and *pol* in cell cultures by using oligonucleotides linked to intercalators. Some PNA sequences bind to double-stranded DNA by an invasion mechanism; two PNA molecules form a triplex structure with the complementary DNA target sequence, whereas the other strand of the DNA duplex is displaced into a single-stranded loop. Once formed, such PNA-DNA complexes are extremely stable. This type of binding is limited to pyrimidine-rich PNA sequences, and therefore B. Norden's team (Chalmers University) is applying spectroscopic techniques to try to understand the mechanism in detail so that it can be extended to direct PNA molecules to any DNA sequence.

An elegant solution to selective targeting of double-stranded DNA was presented by P. Dervan (Caltech). His group designs minor-groove binding polyamides that contain combinations of three different aromatic amino acids, which pair and uniquely recognize each of the four Watson-Crick base pairs (see the figure). Hairpin polyamides bind specifically to predetermined DNA sequences with the affinity and specificity of protein transcription factors. Remarkably, cells are permeable to these polyamides, a property that may be related to the fact that they are significantly smaller in size than oligonucleotide analogs used in antisense approaches. The most recent work shows that these synthetic DNA binding ligands can enter the nucleus and inhibit expression of specific genes by blocking promoter-specific transcription factors.



Deadly hairpins. Hairpin polyamides can be designed to bind double-stranded DNA at any desired base-sequence; upon binding to a promoter sequence the expression of protein from that gene can be blocked. Py, pyrrole; Im, imidazole; and Hp, hydroxypyrrole.

Where is this field going in the next few years? Because pathogen sequence information could lead directly to drug design, C. Cantor (Boston University) suggested that gene-targeting compounds should be an extremely important class of potential therapeutics against unknown biological weapons. P. Dervan argued, however, that the future success for gene-targeted drugs requires continued fundamental research and that more work needs to be done before these revolutionary drugs will be readily available.

References

1. Workshop held 3 to 5 April 1998 at "Friiberghs Herrgàrd." The meeting was sponsored by the Swedish Nobel Foundation for Chemistry and the Swedish National Chemistry Council.

PERSPECTIVES: PROTEIN SYNTHESIS

All You Need Is RNA

Paul Schimmel and Rebecca Alexander

The genetic code is an algorithm that relates triplets of nucleotides called codons—ATG, CGG, CAA, for example—in genes to specific amino acids that, in turn, are linked with one another by peptide bonds to make proteins. Because all of life depends on this algorithm, its chemical basis and that of protein synthesis can tell us something about how life arose on Earth. A significant advance on this front is presented in the article by Nitta *et al.* on page 666 of this issue (*1*). The authors demonstrate that fragments of the ribosome (the organelle that executes the algorithm of the genetic code) containing only RNA are sufficient to catalyze peptide bond synthesis between amino acids, adding weight to the idea that early life systems could have emerged from a world in which RNA molecules coupled amino acids to make peptides (*2*).

The genetic code is established by aminoacylation reactions in which specific amino acids are joined to their cognate transfer RNAs (tRNAs), each of which bears anticodon triplets of the code. The tRNAs are L-shaped (see the figure), with each arm of the L constituting a separate domain. One arm—the acceptor-TψC minihelix—contains the amino acid attachment site at the 3′ end, which has the universal single-stranded sequence CCA, with the amino acid esterified to the terminal A. The other arm of the L contains the anticodon triplet of the code, which is matched to the triplet nucleotide code of the mRNA. This triplet and the amino acid attachment site are separated by 75 angstroms.

The central engine for protein biosynthesis is the ribosome—a large, as yet unsolved, puzzle that makes up more than 25% of the dry mass of the bacteria. The *E. coli* ribosome consists of about 55 proteins and three RNAs—5*S* (120 nucleotides, 16*S* (1542 nucleotides), and 23*S* (2904 nucleotides) ribosomal RNA (rRNA) (*3*). These components are housed in two ribonucleoprotein subunits (large and small). Once aminoacylated, the tRNAs interact with messenger RNAs embedded in the ribosomes. Here the anticodon-containing domains of the tRNAs act as template-reading heads that decode the triplets of the mRNA by codon-anticodon binding. As a result of the lining up of the aminoacylated tRNAs along the mRNA according to the code, the charged minihelix domains are brought together so that the amino group of one amino acid attacks the carbonyl carbon of its neighbor. This coupling reaction occurs at the peptidyl transferase center of the ribosome's large subunit. This functional center is located at a junction of several helices in the fifth of six domains that make

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