orbit their host star at distances closer than Mercury's orbit around the Sun (Fig. 1) — is not unusual for an extrasolar planetary system.

Many similar dense configurations have been detected by the radial-velocity (Doppler) technique since the discovery[7] in 2006 of three Neptune-mass planets on compact orbits around star HD 69830. The Doppler technique measures tiny Doppler shifts in a parent star's light that are caused by the gravitational tug of an orbiting planet. The most dense multi-planet configurations have been observed in a system of seven planets[8] orbiting star HD 10180 and a system of six planets[9] transiting star Kepler-11.

In some dense planetary systems, planets can affect each other through dynamical effects related to their orbits. This phenomenon perturbs the regularity of the orbits, generating small time delays. The delays can be detected with planetary transits and are known as transit-timing variations.

From a combination of the dynamical effect of the planets on their host stars (obtained through Doppler and transit-timing measurements) and transit observations — which measure the dimming of the star as a planet transits it — a planet's mean density can be calculated. This calculation provides insight into the object's overall structure, for example whether it is a gas giant or a small, rocky planet. However, there are few planets below the sub-Saturn mass range for which the density is known. The stars explored by space-based planetary-transit missions such as Kepler are too faint for accurate ground-based Doppler follow-up observations of the smallest planetary candidates, and detection of the timing of the transits is restricted to specific planetary-system configurations[9].

Ideally, the detection of a planet's gravitational tug on its star is required to confirm that a transiting candidate is a planet. Practically, however, for most candidates detected by Kepler, measuring this dynamical effect is challenging. Other possible candidates, including eclipsing two-star systems, can lead to a transiting signal similar to that of a planet, and can be eliminated only through a combination of complementary measurements and statistical analysis. This is the approach that Fressin and colleagues[5] take in their study. Their identification of two Earth-sized planets — Kepler-20 e and Kepler-20 f — relied on a statistical analysis of previous Kepler measurements[6] to establish that the transiting signals are indeed of planetary origin.

To consider the two new planets in the wider planetary landscape, Fressin *et al.* produced a mass–radius diagram of all known 'super-Earth' planets (see Fig. 3 of the paper[5]). A super-Earth is a planet that has a mass between those of Earth and Neptune, irrespective of its internal structure. The diagram is a striking illustration of the potential diversity of planets in this mass domain: objects of the same mass can be a gas giant or a dense, iron-core planet. This result will prompt researchers to explore the origin of such diversity in the context of planet-formation models.

Although the masses of Kepler-20 e and Kepler-20 f are unknown, the authors show[5] that the two planets are without doubt located in the low-end corner of the mass–radius diagram, where Earth-like planets lie. But because the planets' mass is unknown, their composition cannot be determined unambiguously. Interestingly, however, some compositional knowledge exists for Kepler-20 b and Kepler-20 c, from the detection and upper limit of the Doppler signal[6] originating from these two more massive planets. This information already suggests a possible broad range of composition for the two planets: from magnesium silicate to water ice; or they may even be gas giants[6].

The existence of a series of small planets such as Kepler-20 e and Kepler-20 f identify them as key objects in the steadily expanding list of planetary systems. This is because, in contrast to the Solar System, where small, rocky planets lie close to the Sun but gas giants are found far from it, these planets have no obvious hierarchical orbital location. The next, pivotal, step in extrasolar planetary research will be to detect the dynamical effect of each of these small planets on their host star and to determine their mass. ■

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For more on Earth-sized exoplanets, see:
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INFECTIOUS DISEASE

Genomics decodes drug action

Drugs used to treat African sleeping sickness are outdated, and how they enter cells and exert biological effects is poorly understood. A genome-wide study using RNA interference provides valuable insight. SEE LETTER P.232

ALAN H. FAIRLAMB

African trypanosomiasis, or sleeping sickness, is a deadly yet neglected human disease caused by the single-celled parasites *Trypanosoma brucei gambiense* and *T. b. rhodesiense*. The origins of some anti-trypanosome drugs, including suramin and melarsoprol, date back to pioneering studies with coloured dyes and organic arsenical compounds at the beginning of the twentieth century. Nonetheless, the modes of action of these and the three other drugs currently used to treat sleeping sickness (pentamidine, nifurtimox and eflornithine) are incompletely understood. On page 232 of this issue, Alsford *et al.*[1] identify some of the biological pathways used by these drugs, offering insight into how they reach their cellular targets and how drug resistance can arise. The results pave the way for the development of new therapeutic strategies.

The existing antitrypanosome drugs are typically given by injection. Moreover, some of them cannot cross the blood–brain barrier, making them ineffective against late-stage disease, when parasites invade the brain. To facilitate the discovery of drugs that lack these unsatisfactory features, there is a need to identify additional drug targets. With this aim in mind, Alsford *et al.* conducted a genome-wide RNA interference (RNAi) screen on trypanosomes. When induced artificially, RNAi — which works by silencing messenger RNA transcripts[2] — is a powerful tool for probing the biological function of specific genes. It allows researchers to study the cellular effects of the loss of a specific protein, and aids in determining whether a protein has a structural, regulatory, transport or metabolic function.

An inducible RNAi system has previously been set up[3] in *T. brucei* and has already been used for target-based drug discovery, to assess whether specifically selected genes are essential to trypanosome survival[4]. However, this is a relatively slow approach and can suffer from investigator bias. In addition, the sequencing

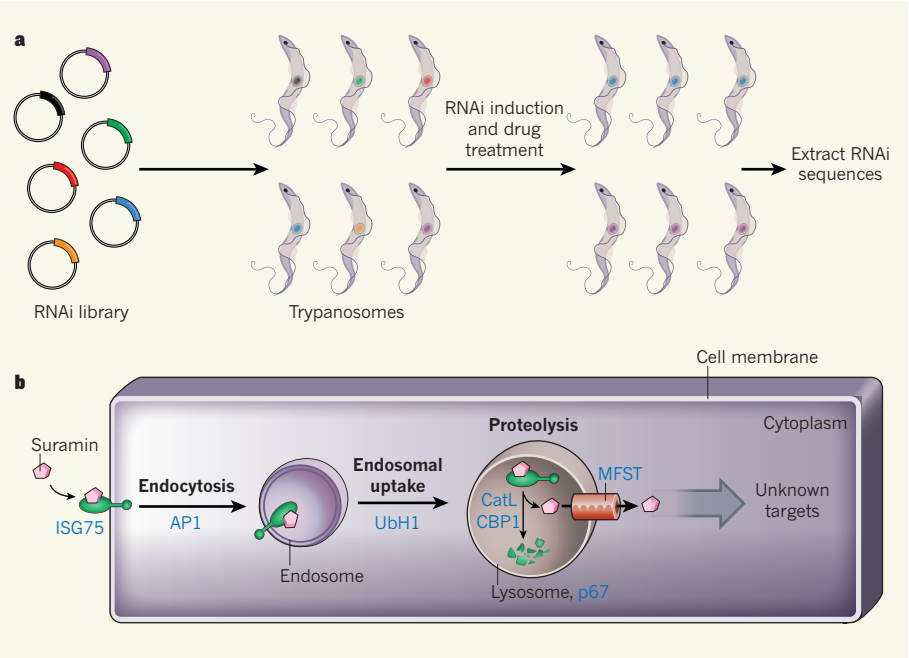

Figure 1 | A genome-wide RNAi screen to identify antitrypanosome drug activity. **a**, By introducing a genome-spanning panel of RNAi molecules into trypanosomes, Alsford *et al.*[1] identified those RNA sequences that, when silenced, allowed the cells to survive treatment with each of five drugs used to treat trypanosomiasis. The authors mapped these sequences onto the trypanosome genome to reveal proteins involved in drug action. Here, trypanosomes containing RNAi sequences that confer resistance to the drug suramin are shown as blue and purple. **b**, Proteins (labelled in blue) pinpointed by the suramin screen are shown as an example of how this technique can reveal stages of the pathway a drug takes, including the drug's entry to the cell by binding to membrane protein ISG75, its uptake into the endosome by endocytosis (which relies on four protein subunits that form adaptor protein complex 1, AP1) and transfer of the suramin–ISG75 complex to the lysosome and its breakdown by proteolysis there (involving the proteins UbH1, CatL, CBP1 and p67). The free drug is then released into the cytoplasm (with the aid of transport protein MFST), where it affects as-yet-unknown targets.

of the *T. brucei* genome[5] allowed application of a genome-wide RNAi screen[6] to examine key features of trypanosome biology. In this method, random fragments of genomic DNA were expressed as inducible RNAi molecules, and the sequence of fragments that, when expressed, caused trypanosome death was determined. This system linked hundreds of previously uncharacterized proteins, some of which may represent new drug targets, to essential functions at various stages of the parasite's life cycle.

Alsford *et al*. have now used the RNAi approach to ask a different question: which non-essential gene products, when down-regulated, confer a selective advantage on drug-treated trypanosomes? The authors conducted the screens with each of the five existing drugs. In response to drug exposure, trypanosome growth was initially curtailed, but a drug-resistant population subsequently emerged. Using high-throughput sequencing, Alsford and colleagues mapped the sequence of each RNAi molecule extracted from these surviving trypanosomes onto the reference genome (Fig. 1a). In such screens, whenever loss of function of a protein increases drug tolerance, its corresponding RNAi target sequence shows up more frequently on the maps than do target sequences for non-essential proteins not conferring a selective advantage.

The current study reveals a fascinating pattern of genes involved in diverse areas of metabolism and cell biology. The authors' screens not only support previous findings from decades of painstaking biochemical and genetic approaches[7], but also reveal previously unknown pathways involved in drug uptake, activation and action.

Knockdown of known or potential drug-uptake mechanisms — through decreased expression of proteins involved in drug transport (for eflornithine and melarsoprol) and cellular uptake[8] (for suramin) — is evident in three of the screens. For suramin, the authors identified multiple proteins that increase resistance to the drug, revealing details of the pathway it follows in trypanosomes (Fig. 1b). They postulate that suramin is initially bound to proteins in the blood plasma and subsequently binds to ISG75, a transmembrane glycoprotein of unknown function on the trypanosome surface. ISG75 is then endocytosed (absorbed by engulfing) by the cell and tagged with the small protein ubiquitin. The ubiquitin tag directs the suramin–ISG75 complex to cellular organelles called lysosomes, where it is broken down by protein-degrading enzymes (CatL and CBP1). This releases suramin, which is then proposed to enter the cell cytoplasm via a transporter protein, MFST, to affect as-yet-unknown intracellular targets.

Alsford *et al.* also discovered an unexpected drug–drug interaction. Knockdown of three enzymes involved in the *de novo* biosynthesis of spermidine, a polyamine compound essential for trypanosome growth, confers resistance to suramin. It also emerged that one of the other drugs, eflornithine, can antagonize suramin's trypanosome-killing activity by inhibiting the synthesis of polyamines.

Of the five drugs studied, nifurtimox differs in that it requires activation by the enzyme nitroreductase to form reactive products, the downstream targets of which remain unknown. Knockdown of nitroreductase (or of its cofactor FMN) leads to resistance to nifurtimox, consistent with previous studies[9]. The nifurtimox RNAi screen also identified reduced synthesis of the electron-transport molecule ubiquinone, suggesting that this is the substrate for nitroreductase in trypanosomes.

Another of the drugs tested, melarsoprol, is an arsenic-based compound that binds to trypanothione, a trypanosome-specific antioxidant metabolite essential to the parasite's survival. The melarsoprol screen shows that resistance to this drug is associated with reduced expression of the transporter protein P2 and with trypanothione biosynthesis, suggesting that the complex formed between trypanothione and melarsoprol is itself toxic.

Cross-resistance — whereby resistance to one drug also confers resistance to another class of drug — occurs between pentamidine and melarsoprol, and other drugs of these respective classes, but, again, the resistance mechanism is unclear. One RNAi effect that Alsford and colleagues hit upon in screens using these drugs identified two closely related aquaglyceroporin proteins. The authors generated trypanosomes lacking these proteins, and found them to be less susceptible to both drugs. This suggests that aquaglyceroporins may be partly responsible for cross-resistance.

Alsford and colleagues' findings[1] should stimulate further research, particularly to determine the functions of other down-regulated genes that encode as-yet-uncharacterized proteins, and other genes and pathways reported in their study. However, not all resistance mechanisms involve loss of protein function — drug-efflux pathways being one example — so these would be missed by RNAi screens. This approach is also unable to identify essential proteins that are drug targets, because targeting these with RNAi leads to cell death.

Therefore, to further unravel the complex mode of action of these drugs, analysis using a genome-wide overexpression system will be required. This method has already been used successfully to demonstrate the effects of

enzyme inhibitors against genetically validated targets such as *N*-myristoyltransferase[10] and trypanothione synthetase[11]. Given the resurgence of interest in screening libraries of chemical compounds for those that inhibit trypanosome growth, to identify novel starting points for drug discovery, a genome-wide strategy would greatly accelerate this expensive and laborious process. ■

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QUANTUM OPTICS

Controlling the light

Means to access and manipulate X-rays have been developing at a slow pace. But quantum-optical effects in ensembles of nuclei offer a way to tackle the control of this energetic radiation. SEE LETTER P.199

BERNHARD W. ADAMS

Our world is one of electrons in chemical bonds, and our sensory perception of it is based on quantum energies of a few electronvolts at most. But during the past century we have uncovered the existence of another realm — that of nuclear physics and electrons in inner atomic shells, where quantum energies fall in the X-ray regime and are of the order of kilo- and mega-electronvolts. Although many applications have been found for X-ray and nuclear science, our ability to control this world has been limited. On page 199 of this issue, Röhlsberger *et al.*[1] demonstrate detailed quantum-physical control of the emission of light occurring at nuclear energy scales. Although this result is unlikely to have an immediate application, new capabilities are expected to emerge from a detailed quantum-level control of X-rays. Among these are types of spectroscopy to probe chemical dynamics, or a drastic reduction in the radiation dose required for biological X-ray applications.

Among some other investigations, such as the control of nuclear γ-ray emission by magnetic fields[2], Röhlsberger and colleagues' study[1] can be seen as a step in a progression towards extending the exquisite control of X-rays and γ-rays. This progression re-traces steps taken previously at lower photon energies than those of X-rays — first with radio-frequency waves, which are of sub-microelectronvolt photon energy and can be easily controlled in amplitude and phase (where a wave's peaks and troughs lie) and, more recently, with near-visible-light lasers, which have photon energies of a few electronvolts. The latter has grown into the field of photonics (smart photons), thanks to progress in precision optics, coherent light sources (those in which light is of well-defined amplitude and phase) and nonlinear optics, which couples light waves instead of allowing them to pass unhindered through each other.

These developments have led to the point at which laser-based high-harmonic generation (HHG) reaches the soft X-ray regime up to about 1 keV. HHG is the nonlinear optical process by which lower-energy photons 'stack up' to generate more energetic ones, and requires meticulous control of the light with respect to coherence and nonlinear optics. Although X-ray and γ-ray photons stand out from thermal or electronic background noise in detectors much more clearly than do visible photons, the development of ways to access and manipulate this energetic radiation has been slow. Now, however, X-ray quantum optics is poised to take off and tackle this radiation regime.

In their study, Röhlsberger *et al.*[1] demonstrate the application of the quantum-optical concepts of superradiance[3] and electromagnetically induced transparency[4] to the control of X-ray scattering. Superradiance is the phenomenon of collective spontaneous emission of radiation. Superradiance, as well as the related effect of subradiance, occurs when an ensemble of atoms or nuclei is prepared in an entangled state (a defining feature of quantum physics) of excitation, and then emits radiation. When the experiment is done such that there is, in principle, no way of telling which atoms or nuclei in the ensemble were excited, it doesn't make sense to consider them individually. Rather, the whole ensemble emits radiation collectively and may show telltale signs of superradiance, namely directional and accelerated light emission. Here, the authors attained X-ray superradiance from a collection of iron-57 nuclei by exciting them with X-rays at a photon energy of 14.4 keV.

To return to the control of light, from radio waves to X-rays, the classical analogue of superradiant directionality is the directional radio signal obtained from a device known as a phased-array antenna, which is commonly used in radar technology. However, in contrast to the phased-array antenna, superradiance occurs even at the extreme quantum limit of ensemble excitation by a single photon[5], as observed in the authors' experiment. At this limit, we cannot speak of the emission of classical waves from many atoms or nuclei undergoing constructive interference. It is the interference of multiple possible excitation–emission pathways for a single photon that leads to collective emission. Given the right tools, this interference can be controlled.

One of these tools is electromagnetically induced transparency (EIT), in which light absorption due to a transition from one atomic energy level, *g*, to another, *e*, is suppressed as a result of coherence induced by an auxiliary laser. In the typical case, a laser strongly drives a transition from *e* to a metastable state, *f*, and back to *e*; this is technically known as Rabi flopping, and occurs at the Rabi frequency, which is proportional to the square root of the auxiliary-laser intensity. Rabi flopping leads to a splitting of *e*, so that there are now two levels (sidebands) at energies symmetrically above and below that of *e*. For incident photons at the original transition energy from *g* to *e*, the contributions of the two sidebands to the absorption cancel out.

In their experiment, the authors[1] observed superradiance from ^{57}Fe nuclei in an X-ray waveguide because X-ray emission from the nuclei interferes constructively with that from their mirror images in the waveguide walls. The strength of this collective emission of the nuclei, together with their images, depends on the coupling to the guided mode — that is, on the position of the nuclei relative to the standing-wave X-ray pattern that is created in the waveguide. In a configuration in which one layer, A, of nuclei is coupled strongly to a guided mode and another layer, B, is not, they also detected a sharp dip in the ensemble's absorption spectrum characteristic of EIT. No auxiliary laser was used to couple between two energy levels, as in conventional EIT. Instead, excitations of the nuclear ensembles A and B correspond, respectively, to those of states *e* and *f* in conventional EIT, and the coupling of the two is due to the waveguide. In this case, ensemble B, which lacks superradiance owing to its weak waveguide coupling, takes the role of the metastable state *f* because it has a longer excited-state