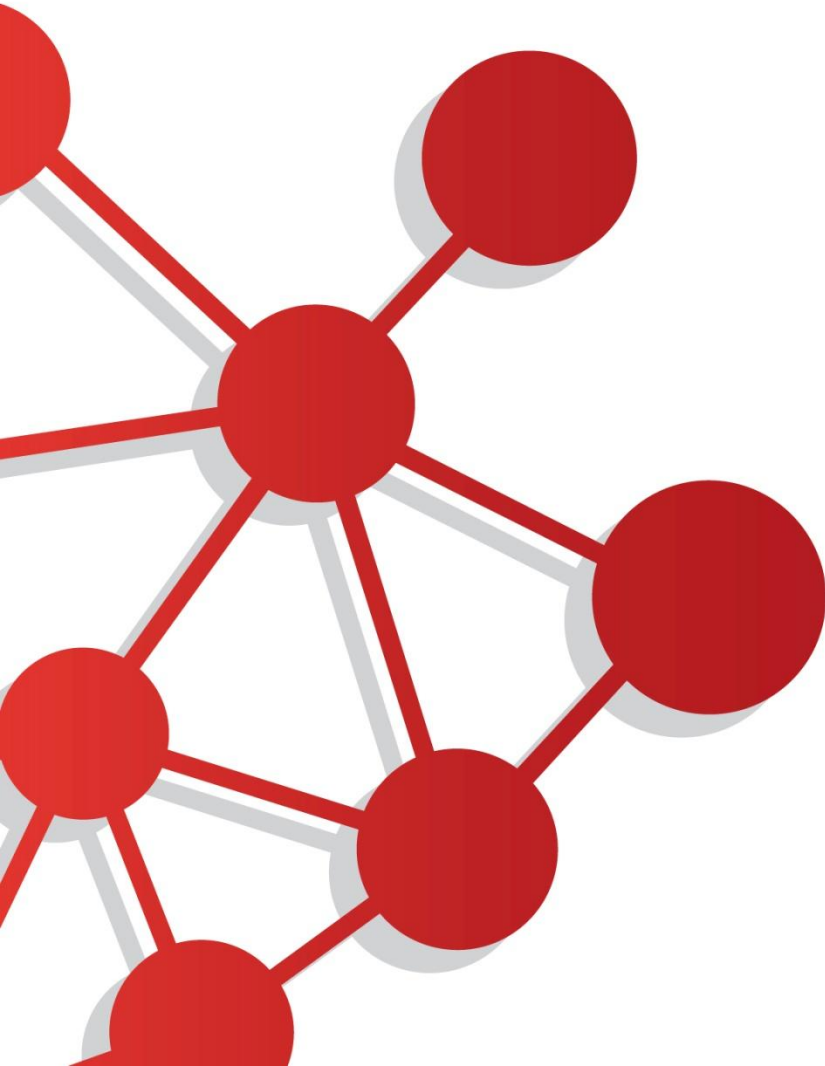


The many elements to the article of the future

Jason Wilde

Nature Publishing Group

15th October 2012



Article of the future...

- Evolution of research
- Publishing technology
- Beyond [the] paper
- External data/information
- Text, data, metadata
- The article of the future...
- The end..?



Evolution of research

no. 6216 April 25, 1953 NATURE 737

equipment, sent to Dr. G. E. R. Duncanson and the captain and officers of R.H.S. Discovery II for their part in making the observations.

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MOLECULAR STRUCTURE OF NUCLEIC ACIDS

A Structure for Deoxyribose Nucleic Acid

WE wish to suggest a structure for the salt of deoxyribose nucleic acid (D.N.A.). This structure has novel features which are of considerable biological interest.

A structure for nucleic acid has already been proposed by Pauling and Corey¹. They kindly made their manuscript available to us in advance of publication. Their model consists of three intertwined chains, with the phosphates near the fibre axis, and the bases on the outside. In our opinion, this structure is unsatisfactory for two reasons: (1) We believe that the material which gives the X-ray diagram is the salt, not the free acid. Without the acidic hydrogen atoms it is not clear what forces would hold the structure together, especially as the negatively charged phosphates near the axis will repel each other. (2) Some of the van der Waals distances appear to be too small.

Another three-chain structure has also been suggested by Frazer (in the press). In his model the phosphates are on the outside and the bases on the inside, linked together by hydrogen bonds. This structure as described is rather ill-defined, and for this reason we shall not comment on it.

We wish to put forward a radically different structure for the salt of deoxyribose nucleic acid. This structure has two helical chains each coiled round the same axis (see diagram). We have made the usual chemical assumptions, namely, that each chain consists of phosphate diester groups joining β -D-deoxy-ribofuranose residues with 3',5' linkages. The two chains (but not their bases) are related by a dyad perpendicular to the fibre axis. Both chains follow right-handed helices, but owing to the dyad the sequences of the atoms in the two chains run in opposite directions. Each chain loosely resembles Pauling's model No. 1; that is, the bases are on the inside of the helix and the phosphates on the outside. The configuration of the sugar and the atoms near it is close to Pauling's 'standard configuration', the sugar being roughly perpendicular to the attached base. There

is a residue on each chain every 3.4 Å, in the z-direction. We have assumed an angle of 36° between adjacent residues in the same chain, so that the structure repeats after 10 residues on each chain, that is, after 34 Å. The distance of a phosphate atom from the fibre axis is 10 Å. As the phosphates are on the outside, residues have easy access to them.

The structure is an open one, and its water content is rather high. At lower water contents we would expect the bases to lie so that the structure could become more compact.

The novel feature of the structure is the manner in which the two chains are held together by the purine and pyrimidine bases. The planes of the bases are perpendicular to the fibre axis. They are joined together in pairs, a single base from one chain being hydrogen-bonded to a single base from the other chain, so that the two lie side by side with identical z-co-ordinates. One of the pair must be a purine and the other a pyrimidine for bonding to occur. The hydrogen bonds are made as follows: purine position 1 to pyrimidine position 1; purine position 6 to pyrimidine position 6.

If it is assumed that the bases only occur in the structure in the most plausible tautomeric forms (that is, with the keto rather than the enol configuration) it is found that only specific pairs of bases can be held together. These pairs are: adenine (purine) with thymine (pyrimidine), and guanine (purine) with cytosine (pyrimidine).

In other words, if an adenine forms one member of a pair, on either chain, then on the other assumption the other member must be thymine; similarly for guanine and cytosine. The sequences of bases on a single chain does not appear to be restricted in any way. However, if only specific pairs of bases can be formed, it follows that if the sequence of bases on one chain is given, then the sequence on the other chain is automatically determined.

It has been found experimentally^{2,3} that the ratio of the amounts of adenine to thymine, and the ratio of guanine to cytosine, are always very close to unity for deoxyribose nucleic acid.

It is probably impossible to build this structure with a ribose sugar in place of the deoxyribose, as the extra oxygen atom would make too close a van der Waals contact.

The previously published X-ray data^{4,5} on deoxyribose nucleic acid are insufficient for a rigorous test of our structure. So far as we can tell, it is roughly compatible with the experimental data, but it must be regarded as unproved until it has been checked against more exact results. Some of these are given in the following communications. We were not aware of the details of the model presented there when we devised our structure, which rests mainly though not entirely on published experimental data and stereochemical arguments.

It has not escaped our notice that the specific pairing we have postulated immediately suggests a possible copying mechanism for the genetic material.

Full details of the structure, including the conditions assumed in building it, together with a set of co-ordinates for the atoms, will be published elsewhere.

We are much indebted to Dr. Jerry Doolittle for constant advice and criticism, especially on interatomic distances. We have also been stimulated by a knowledge of the general nature of the unpublished experimental results and ideas of Dr. M. H. F. Wilkins, Dr. R. E. Franklin and their co-workers at



The fibre is purely helical, with the two chains twisted about the same axis. The bases are on the inside of the helix and the phosphates on the outside. The configuration of the sugar and the atoms near it is close to Pauling's 'standard configuration', the sugar being roughly perpendicular to the attached base. There

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DNA Structure 1953

1 Page

2 Authors

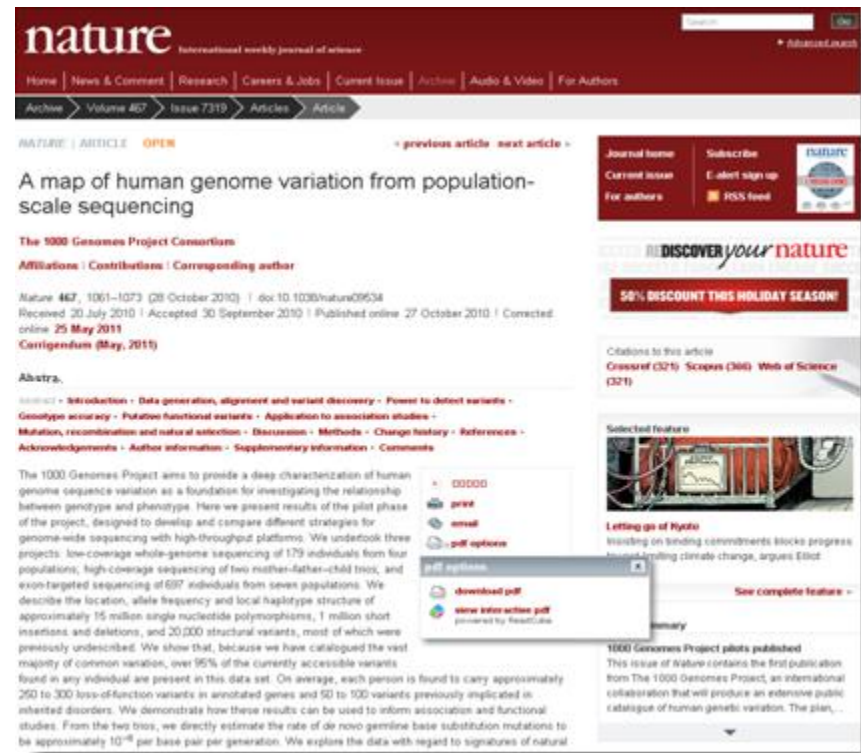
1 Figure

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Evolution of research

1000 Genome Project 2010

12 page, 76 Institutions, 12,145 SRA run ids



Evolution of research

Encode Project 2012

30 papers, 3 Journals

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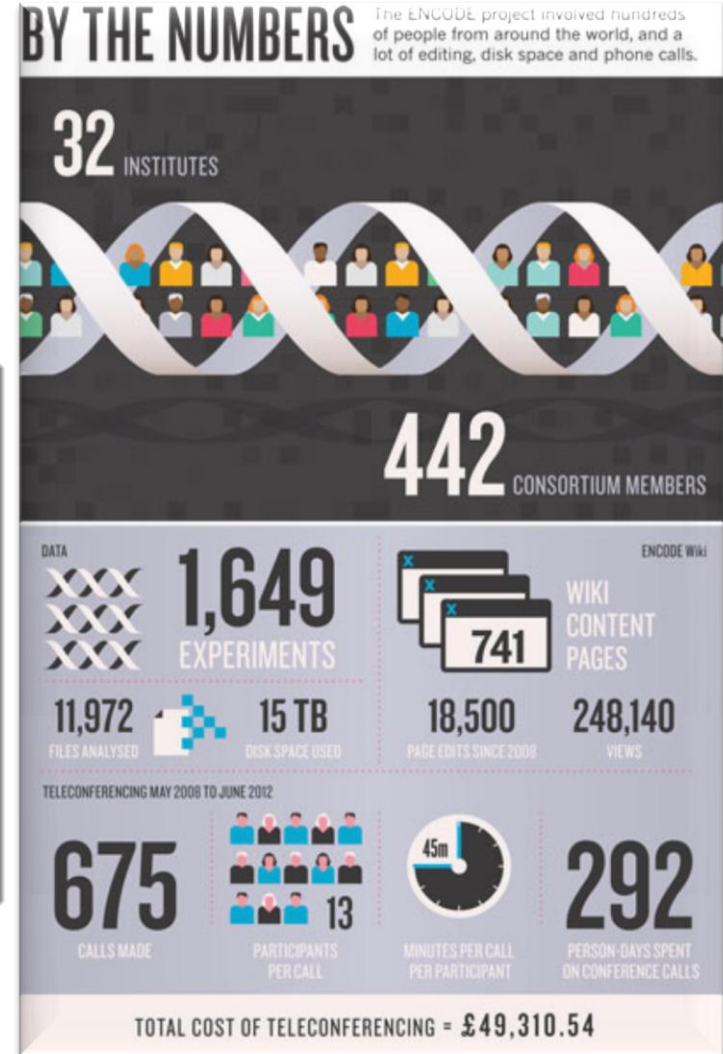
THREADS
Epigenetic regulation of RNA processing
Thread 5 of 13
ENCODE data explores properties of RNA processing and its relationship to histone modifications.

PAPERS
This thread consists of papers from the following papers:
- An integrated encyclopedia of DNA elements in the human genome
- Chromatin and gene activity in human cells
- Deep sequencing of individual RNA transcripts reveals features of the transcriptome
- Deep X-seq
- Epigenetic gene expression: many changes are not in the DNA sequence

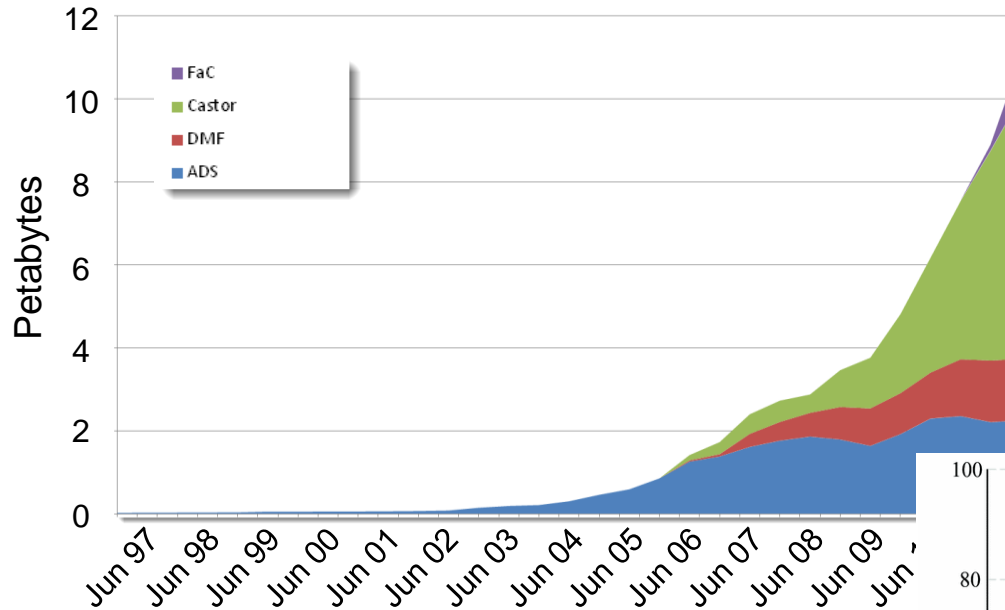
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Select a thread to start

Guide to the ENCODE explorer

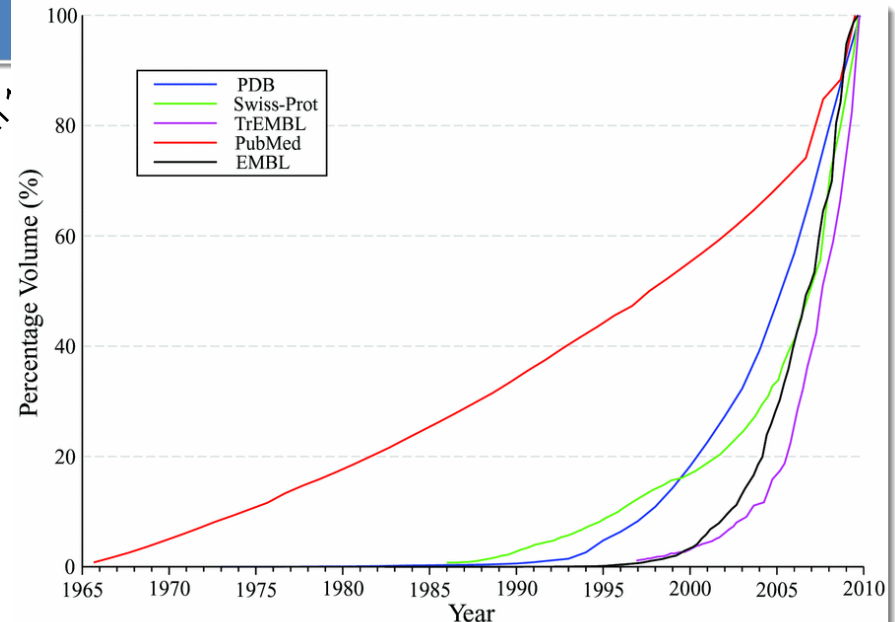


Evolution of research



- **CERN** high energy physics data from the Atlas, LHCb, CMS and Alice. These data are stored using the CERN designed **Castor** infrastructure
- **Castor** is also used to store data from STFC's UK facilities (**FaC**).
- **ADS** is the old archive with lots of small backups.
- **DMF** includes the preserved documents from the CEDA Repository at the British Atmospheric Data Centre, and Tesella Safety Deposit Box (SDB) services to preserve data collected on the ISIS, Diamond and CLF facilities.

Graphical illustration of the growth of biomedical research publications (**red**; current total >19 million), alongside the accumulation of research data, including nucleic acid sequences (**black**; current total ~163 million), computer-annotated protein sequences (**magenta**; current total 9 million), manually annotated protein sequences (**green**; current total 500000) and protein structures (**blue**; current total 60000)



Publishing technology



NATURE
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"Is the solid ground
Of Nature made the mind which builds for you" — WEAVERMAN

THURSDAY, NOVEMBER 4, 1869

NATURE: APHORISMS BY GOETHE
NATURE! We are surrounded and embraced by her; powerless to separate ourselves from her, and powerless to penetrate beyond her. Without asking, or warning, she snatches us up into her circling dance, and whisks us on until we are tired, and drop from her arms. She is ever shaping new forms: what is, has never yet been; what has been, comes not again. Everything is new, and yet nought but the old. We live in her midst and know her not. She is incessantly speaking to us, but betrays not her secret. We constantly act upon her, and yet have no power over her.

The one thing she seems to aim at is Individuality; yet she cares nothing for individuals. She is always building up and destroying; but her workshop is inaccessible.

Her life is in her children; but where is the mother? She is the only artist; working up the most uniform material into steepest opposites; arriving, without a trace of effort, at perfection, at the most exact precision, though always veiled under a certain softness.

Each of her works has an essence of its own; each of her phenomena a special characterisation; and yet their diversity is in unity.

She performs a play; we know not whether she sees it herself, and yet she acts for us, the lookers-on.

Incessant life, development, and movement are in her, but she advances not. She changes for ever and ever, and rests not a moment. Quietude is inconceivable to her, and she has laid her curse upon rest. She is firm. Her steps are measured, her exceptions rare, her laws unchangeable.

She has always thought and always thinks; though not as a man, but as Nature. She broods over an all-comprehending idea, which no searching can find out.

Mankind dwell in her and she is in them. With all men she plays a game for love, and rejects the more they win. With many, her moves are so hidden, that the game is over before they know it.

That which is most unmaterial is still Nature; the stupidest philistinism has a touch of her genius. Whoso cannot see her everywhere, sees her nowhere rightly.

She loves herself, and her innumerable eyes and affections are fixed upon herself. She has divided herself that she may be her own delight. She causes an endless succession of new capacities for enjoyment to spring up, that her insatiable sympathy may be assuaged.

She rejoices in illusion. Whoso destroys it in himself and others, him she punishes with the sternest tyranny. Whoso follows her in faith, him she takes as a child to her bosom.

Her children are numberless. To none is she altogether mighty; but she has her favourites, on whom she squanders much, and for whom she makes great sacrifices. Over greatness she spreads her shield.

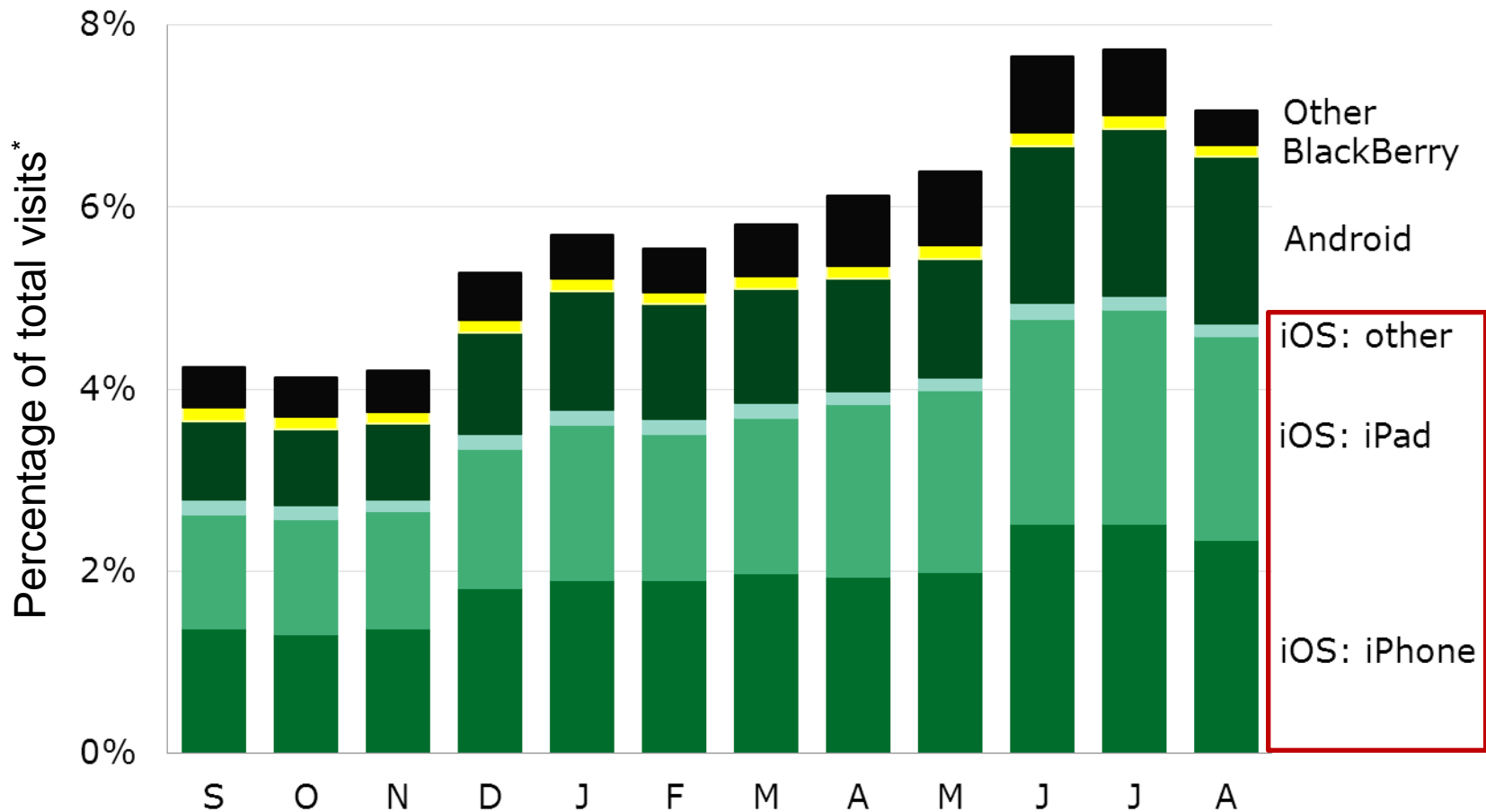
She tosses her creatures out of nothingness, and tells them not whence they came, nor whither they go. It is their business to run, she knows the road. Her mechanism has few springs—but they never wear out, are always active and manifold.

The spectacle of Nature is always new, for she is always renewing the spectators. Life is her most exquisite invention; and death is her expert contrivance to get plenty of life.

She ways man in darkness, and makes him for ever long for light. She creates him dependent upon the earth, dull and heavy; and yet is always shaking him until he attempts to soar above it.

It used to be so very simple...

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ARTICLE

doi:10.1038/nature09534

A map of human genome variation from population-scale sequencing

The 1000 Genomes Project Consortium*

The 1000 Genomes Project aims to provide a deep characterization of human genome sequence variation as a foundation for investigating the relationship between genotype and phenotype. Here we present results of the pilot phase of the project, designed to develop and compare different strategies for genome-wide sequencing with high-throughput platforms. We undertook three projects: low-coverage whole-genome sequencing of 179 individuals from four populations; high-coverage sequencing of two mother-father-child trios; and exon-targeted sequencing of 697 individuals from seven populations. We describe the location, allele frequency and local haplotype structure of approximately 15 million single nucleotide polymorphisms, 1 million short insertions and deletions, and 20,000 structural variants, most of which were previously undescribed. We show that, because we have catalogued the vast majority of common variation, over 95% of the currently accessible variants found in any individual are present in this data set. On average, each person is found to carry approximately 250 to 300 loss-of-function variants in annotated genes and 50 to 100 variants previously implicated in inherited disorders. We demonstrate how these results can be used to inform association and functional studies. From the two trios, we directly estimate the rate of *de novo* germline base substitution mutations to be approximately 10^{-8} per base pair per generation. We explore the data with regard to signatures of natural selection, and identify a marked reduction of genetic variation in the neighbourhood of genes, due to selection at linked sites. These methods and public data will support the next phase of human genetic research.

Understanding the relationship between genotype and phenotype is one of the central goals in biology and medicine. The reference human genome has provided a foundation for understanding significantly to the genetic architecture of disease, but it has not yet been possible to study them systematically. Meanwhile, advances in DNA

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Beyond [the] paper

Methods

Abstract • Introduction • Results • Discussion • Methods • References • Acknowledgments • Author information • Supplementary information

Mice and LCMV.

All mouse strains were maintained in specific pathogen-free conditions in the animal facilities at the University of Massachusetts Medical School (UMMS). All experiments involving live animals were approved by and performed in accordance with guidelines set forth by the UMMS Department of Animal Medicine and the Institutional Animal Care and Use Committee. C57BL/6J, B6.PL-Thy1a/Cy J (Thy1.1), B6;129S2-*Tap1^{tm1AtpJ}* (*Tap1⁰*), C57BL/6-Tg(CAG-OVA)₉₁₆JenJ (OVA transgenic) were from Jackson Labs. *B2i-nu11* (MECL1)¹⁰, *β1i-nu11* (LMP2)¹¹, *β5i-nu11* (LMP7)¹² and C57LJ-L^{Tg} Background strain characterization of fully bacal polymorphisms spanning the genome) was performed in the UMMS Biocontainment Suite described²¹. Mice were infected intraperitoneally considered immune after at least 6 weeks.

Immunoblotting.

Spleen lymphocytes were lysed in radioimmunoprecipitation buffer with Complete-Mini protease inhibitor cocktail (Roche). Loading of lysates was normalized by protein concentration (Pierce BCA Protein Assay kit). Spleen proteasomes were isolated as described¹. Primary antibodies anti-LMP2 (ab3328, Abcam), anti-LMP7 (ab3323, Abcam), anti- α 1+2+3+5+6+7 (MCP231, Abcam), anti-Tap1 (sc-11464, Santa Cruz Biotechnology), anti-GAPDH (MAB374, Millipore) or anti-ubiquitin (Z0458, Dako) were followed with horseradish peroxidase-conjugated secondary antibody (111-035-144 or 115-035-003, Jackson Immunochemicals). Chemiluminescence (Thermo Scientific SuperSignal West Pico or Millipore Immobilon Western HRP Substrates) was detected with X-ray film. The images were optimized with Photoshop Autolevels.

Quantification of Tap1 mRNA.

RNA was harvested with the Qiagen RNeasy kit, treated with Ambion DNA-free reagent (Ambion) and quantified with a Nanodrop spectrophotometer. RNA (1 μ g) was then reverse-transcribed with the iScript cDNA synthesis kit (BioRad). TaqMan 2 \times Master Mix and Tap1 and Actb (β -actin) Primer/Probe sets (ABI) were used for quantitative PCR on a BioRad iCycler.

Flow cytometry analysis of naive mice.

Lymphocytes (from blood, spleen, thymus or axil, brachial, inguinal and cervical lymph nodes) were blocked with anti- $Fc\gamma$ receptor (24G2, ATCC) before being stained with anti-B220 (RA3-6B2, eBioscience), anti-CD3e (145-2C11, BD Pharmingen) or anti-CD3 molecular complex (17A2, BD Pharmingen); anti-CD4 (RM4-5, BD Pharmingen); anti-CD8 α (53-6.7, BD Pharmingen); anti-CD11b (M1/70, eBioscience); anti-CD11c (N418, eBioscience); anti-H-2K^b (AF6-88.5, BD Pharmingen) or anti-H-2D^b (KH95, BD Pharmingen); and anti-TCR β (h57-597, eBioscience).

Cell lines.

11p9Z has been described²³. For RF33.70-LUC, RF33.70 cells²⁶ were transduced with NFAT-luciferase (from pGL3-NFAT²², Addgene 17870) and the *bsd^R* blastocidin resistance gene (pCDNA6, Invitrogen) driven by the SV40 promoter (pCDNA3.1 hygro⁺, Invitrogen) cloned into pCDH1 (Systems Bioscience), replacing the CMV promoter (as VSV-G pseudotyped lentivirus). For 12.64-CD8 α -LUC, 12.64 cells²⁵ were transduced first with pBMN-IRES-Ly2a (ref. 33; as VSV-G pseudotyped retrovirus, <http://www.stanford.edu/group/holan/>), then with pTRIPZ (Open Biosystems) in which the red fluorescent protein had been replaced with CD8 α (cloned from mouse spleen cDNA) and finally with pCDH1-NFAT-Luc-Bsd (as lentivirus). Hybridoma culture media was RPMI 1640 with 10% vol/vol FBS, 2 mM L-glutamine, 10 mM HEPES, 1 \times MEM nonessential amino acids (Gibco) and 55 μ M β -mercaptoethanol (Sigma). 12.64-CD8 α -LUC cells were treated with 1 μ g/ml doxycycline (Clontech) for 16–24 h before use.

In vitro antigen presentation.

Bone marrow cells were matured for 6–7 d with granulocyte-macrophage colony-stimulating factor (Invitrogen, 10 ng/ml) and interleukin 4 (IL-4; 5 ng/ml, Invitrogen or eBioscience). For H-Y proliferation, 3×10^4

deficient hosts. Moreover, we also found no defect in CD4⁺ T cell numbers or responses in naive or LCMV-infected animals. In addition to the differences we observed in the presentation of 9 of 11 immunogenic epitopes, we found that the peptide repertoire of triply deficient animals was qualitatively and substantially different from those of wild-type or any singly deficient mice, as demonstrated by the robust rejection of wild-type cells by triply deficient animals.

It is noted that rejection of the wild-type cells was unlikely to be minor histocompatibility differences because the triply deficient animals were fully backcrossed. In addition, such histocompatibility differences would be expected to elicit bidirectional responses between the strains, but we found no rejection of triply deficient cells by wild-type animals. Instead, this 'one-way' rejection suggested that wild-type animals presented a substantially different set of peptides than those found in triply deficient animals, containing peptides generated by both immunoproteasomes and constitutive proteasomes. Notably, consistent with these results, comparison of the peptides eluted from matched samples of MHC class I molecules on wild-type and triply deficient splenocytes revealed that only about one-half of the peptides from both H-2D^b and H-2K^b samples were shared between the two strains. This was probably an underestimate because the mass spectrometry analysis detects the presence of abundant peptides but not their precise amount. Therefore, even among the peptides that were presented in both the wild-type and triply deficient mice, there were probably quantitative differences, as we found such differences in the presentation of the majority (9 of 11) of immunogenic epitopes in quantitative assays. Comparing the peptides we identified as unique to immunoproteasome-deficient mice against a larger data set of BL6-presented peptides from the literature, we found that 75–80% were still present only in the triply deficient pools³¹. The 20–25% of additional 'shared' peptides could have been generated by constitutive proteasomes in wild-type preparations from the published studies and/or could represent the detection of lower-abundance peptides in published analyses.

Together, these results demonstrated the importance of immunoproteasomes in generating peptides for MHC class I antigen presentation, a contribution that has been substantially underestimated. A potentially important implication of our findings was that under noninflammatory conditions the peptides presented by DCs, which constitutively express immunoproteasomes, will be substantially different from the ones displayed on parenchymal cells, which contain only constitutive proteasomes. Therefore, T cell responses stimulated by DCs may not optimally recognize parenchymal cells until immunoproteasomes are induced in the latter by interferon. This may lower the effectiveness of CD8⁺ T cell immunity in situations where IFN- γ is not produced. Similarly, this could help pathogenic cells that do not respond to IFN- γ and/or express immunoproteasomes, such as some tumors or cells infected with viruses that inhibit IFN- γ responses, evade immune responses.

METHODS

Methods and any associated references are available in the online version of the paper at <http://www.nature.com/natureimmunology/>.

Note: Supplementary information is available on the Nature Immunology website.

ACKNOWLEDGMENTS

We thank J. Monaco (University of Cincinnati) for *B2i*-deficient mice, L. Van Kaer (Vanderbilt University School of Medicine) for *β1i* singly deficient mice; C. Perreault (University of Montreal), with permission from H. J. Feltham (University Clinics Urm) for *β5i* singly deficient mice; R. Fox (UK; US National Institutes of Health) for C57BL/6 H-Y-transgenic mice; N. Shastri (University of California, Berkeley) for 11p9z cells; E. Raines (University of Washington) for

VOLUME 13 NUMBER 2 FEBRUARY 2012 NATURE IMMUNOLOGY

Beyond [the] paper

PROTOCOL

Assay of protein kinases using a protocol

C James Hastie^{1,3}, Hilary J McLauchlan^{1,3} & Philip Cohen²

¹Division of Signal Transduction Therapy and ²Medical Research Council Protein Phosphorylation Unit, University of Dundee, Dow Street, Dundee DD1 5BI, Scotland. ³These authors contributed equally. (p.cohen@dundee.ac.uk).

Published online 3 August 2006; doi:10.1038/nprot.2006.149

Protein kinase activity results in the incorporation of radiolabeled phosphate. The measurement of the amount of radioactivity incorporated into a substrate enzyme activity to be quantified. The activity is expressed as a 'unit', where 1 catalyzes the incorporation of 1 nanomole of phosphate into the standard substrate of activity per milligram protein. The assay format described here is quick, simple, direct measurement of activity and remains the 'gold standard' for the quantification of activity, and the assay takes one person less than 1 hour to complete.

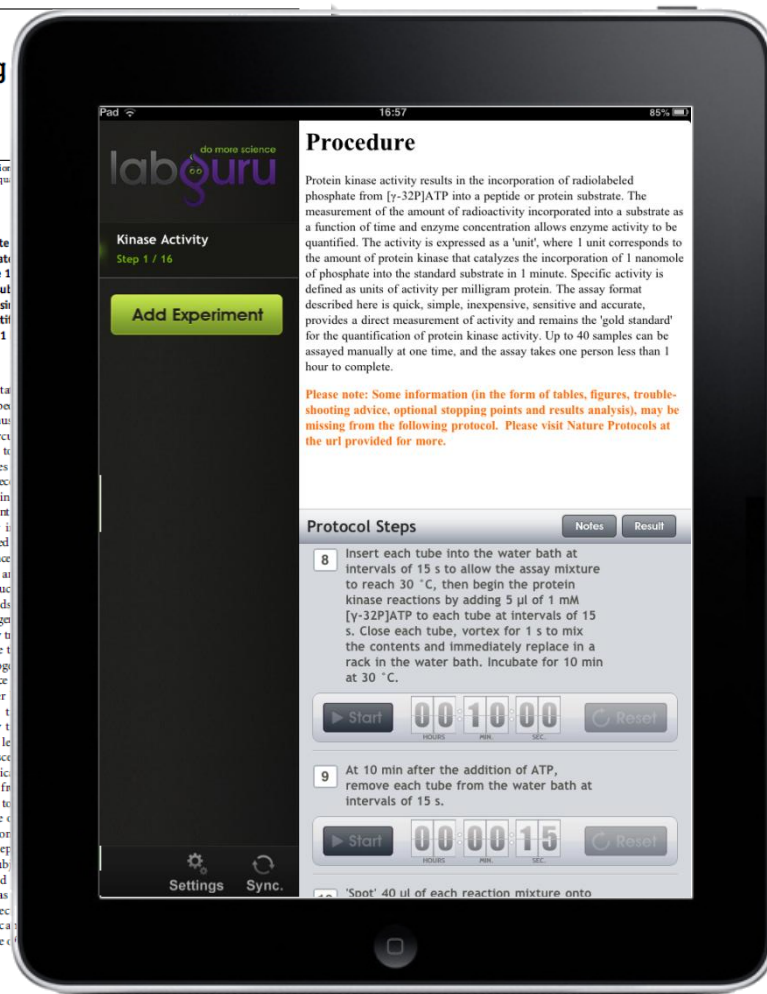
INTRODUCTION

The attachment and removal of phosphate from proteins, called 'reversible phosphorylation', is catalyzed by two classes of enzyme, called 'protein kinases' and 'protein phosphatases'. Protein phosphorylation regulates nearly all aspects of cell life, and protein kinases are the largest single family of enzymes encoded by the human genome, with over 500 members. Abnormal protein phosphorylation is a cause or a consequence of major diseases worldwide, including cancer, diabetes and chronic inflammatory diseases. For that reason, protein kinases have become the second most highly studied class of drug target, behind G protein-coupled receptors (GPCRs), and are a chief area of research for both academic laboratories and the pharmaceutical industry¹. Protein kinases catalyze the phosphorylation of serine, threonine, tyrosine and histidine residues on their target proteins, a reaction that involves the transfer of the γ -phosphoryl group of ATP to the amino acid side chain according to the following chemical equation: $Mg\text{-ATP} + \text{protein} + \text{protein kinase} \rightarrow \text{phosphorylated protein} + Mg\text{-ADP} + \text{protein kinase}$.

Protein kinase activity is measured most conveniently using radiolabeled [γ -³²P]ATP and an appropriate acceptor peptide or protein substrate. The assay method described here was initially developed in the late 1970s and involves the use of phosphocellulose paper squares to capture the phosphorylated peptides or proteins resulting from the protein kinase reaction^{2,3}. The papers are immersed in phosphoric acid to convert the acceptor peptides and proteins to positively charged species which bind quantitatively to the negatively charged phosphocellulose paper⁴. The papers are washed extensively in phosphoric acid to remove all the [γ -³²P]ATP substrate included in the assay. ATP, being negatively charged, does not adhere to the phosphocellulose papers and is washed away, leaving only radiolabeled product bound to the papers, which can then be measured.

This method can be used to study the phosphorylation of all proteins that are phosphorylated on serine, threonine and tyrosine residues, except the extremely few proteins that would not be positively charged at a pH of 1.8. Small peptide substrates should have a charge of at least +2 (and ideally +3) at a pH of 1.8 to bind

quantitatively to the phosphocellulose paper. The assay is described in terms of a pH of 1.8. Small peptide substrates should have a charge of at least +2 (and ideally +3) at a pH of 1.8 to bind



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NATURE CHEMISTRY

A biomimetic molecule ligand

Claudio Aquino, Moh Glenn C. Micalizio

Affiliations | Contrib

Nature Chemistry 4, 9
Received 21 June 2011

Highlighting tool

Compounds

Abstract

Abstract | Main | Results
Supplementary informati

The discovery of new protein function often is widely recognized through protein ligands. Much like libraries, yet the synthesis by one or more of the fragments conformational heterogeneity infrastructure of moderate complexity describe the design and emerging principles associated with the structure of polyketide-conformationally constrained molecules which offers compatibility demonstrate that a COF identifying a non-covalent

Subject terms: Chem

NATURE CHEMISTRY DOI: 10.1038/NCHEM1200 ARTICLES

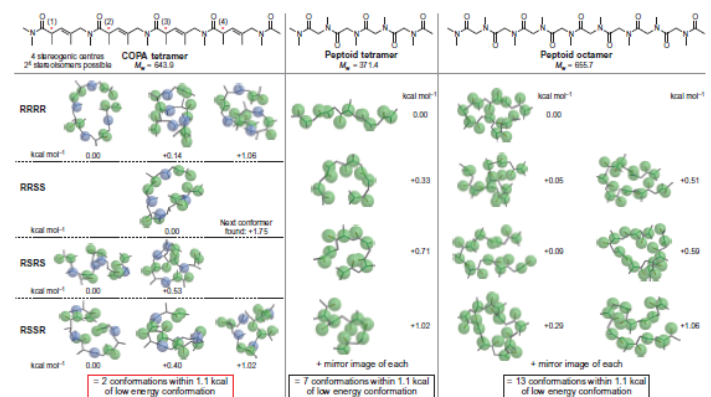


Figure 2 | Stereochemistry of the COPA backbone is anticipated to have a substantial impact on skeletal shape and the disposition of side chains in space. Distribution of conformers found within 1.1 kcal mol⁻¹ of the lowest-energy conformation identified. Calculations were conducted with Spartan-08/MMFF model/Conformer Distribution option/Monte Carlo algorithm. Coloured spheres highlight the relative position of heteroatoms (green) and alkenes (blue). Although these molecular mechanics calculations are not interpreted to predict the solution-phase structure of these oligomers, the calculations provide a uniform lens through which to observe unique characteristics associated with this new class of synthetic oligomers.

double asymmetric relationships between amine 11 and acid 1 have little impact on chemical efficiency for this bond construction—a critically important virtue of this chemistry, as split-and-pool techniques will aim to prepare all combinations of stereochemistry along the growing COPA backbone. With regard to this later consideration associated with the projected application of this chemistry in split-and-pool format, we recognize that oligomerization of chiral monomers of 90% e.e. will result in the production of minor diastereomers on each bead. The combinatorial nature of this process, however, will ensure that the population contains beads that present these minor impurities as major constituents. In this way, a built-in control mechanism exists to aid in the analysis of assay results, as the minor component on any particular bead will be present as a major component on a different bead within the collection. That said, we anticipate that conformations can be found in future studies to crystallize intermediate 7 or 8 as a means to attain isomeric homogeneity.

Establishing the value of COPA libraries as a source of protein ligands. Moving forward to explore the utility of COPA oligomers as a potential source of protein ligands, a library of tetramers was prepared by split-and-pool methods. To be compatible with our on-bead screening platform¹¹, we selected 160 μm Tentagel beads functionalized with a tetrameric polyamide (Fig. 3a), the structure of which was selected to optimize subsequent MS-based structure elucidation (see Supplementary Information for details). Targeting a library of 160,000 members, we used ten primary amines and two pentenoic acids as depicted in Fig. 3a. As we planned to carry out structural elucidation by MS, we used a heavy atom label (CD₂ at C2) to correlate differences in the mass of fragment ions with absolute stereochemistry of the chloropentenoic acid monomer. Alongside these efforts, a library of peptoid tetramers

was prepared with the same amines used for the COPA library (Fig. 3f) in an effort to establish a baseline for comparison between these two synthetic oligomer platforms. Matrix assisted laser desorption/ionization (MALDI) mass spectra revealed a single strong peak for the COPAs released from several individual beads chosen randomly from the library, indicating that each bead predominantly displays a single compound and that each synthetic step proceeded in high yield.

Having established that the library was of high quality, it was screened against the DNA-binding domain of p53, an important transcription factor that regulates a variety of genes involved in cell cycle control and apoptosis. More than half of human cancers express inactive p53 due to the presence of missense mutations in the DNA-binding domain (DBD) that destabilize the folding of the protein¹². There is considerable interest in the identification of 'chemical chaperones'¹³ whose binding to p53 might stabilize the wild-type, functional, folded conformation¹⁴. Because transcription factors are generally considered to be extremely challenging targets for small molecules¹⁵, we considered p53 recognition a stringent test of the utility of this new class of compounds.

Purified, bacterially expressed, FLAG-tagged p53-DBD (10 μM) was incubated with the bead-displayed COPA library in the presence of high levels of competitor proteins to suppress non-specific binding events. The beads were then washed and treated with anti-FLAG antibody followed, after another washing step, by anti-IgG antibodies conjugated to red quantum dots. The beads were then examined under a low-power fluorescent microscope. Several beads with a strong red halo surrounding them, indicating binding of the quantum dot via the p53-FLAG/anti-FLAG antibody/anti-IgG-quantum dot sandwich complex, were observed (Fig. 4a). These, as well as some beads with weaker staining, were picked using a micropipette. In all, 22 beads were collected. Six of

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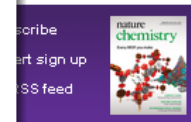
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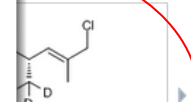
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NATURE CHEMICAL BIOLOGY | ARTICLE

Regulation of CK2 by phosphorylation and O-GlcNAcylation revealed by semisynthesis

Mary Katherine Tarrant, Hee-Sool Rho, Zhi Xie, Yu Lin Jiang, Christopher Gross, Jeffrey C Culhane, Gai Yan, Jiang Qian, Yoshitaka Ichikawa, Tatsuji Matsuoka, Natasha Zachara, Felicia A Etzkorn, Gerald W Hart, Jun Seop Jeong, Seth Blackshaw, Heng Zhu & Philip A Cole

[Affiliations](#) | [Contributions](#) | [Corresponding author](#)

Nature Chemical Biology (2012) | doi:10.1038/nchembio.771
Received 12 August 2011 | Accepted 24 October 2011 | Published online 22 January 2012

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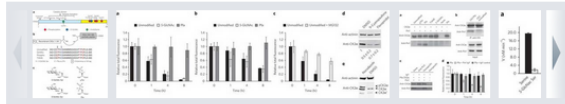
Compounds Genes and Proteins

Abstract

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Protein serine-threonine kinase casein kinase II (CK2) is involved in a myriad of cellular processes including cell growth and proliferation through its phosphorylation of hundreds of substrates, yet how CK2 function is regulated is poorly understood. Here we report that the CK2 catalytic subunit CK2 α is modified by O-linked β -N-acetyl-glucosamine (O-GlcNAc) on Ser347, proximal to a cyclin-dependent kinase phosphorylation site (Thr344). We use protein semisynthesis to show that phosphorylation of Thr344 increases the cellular stability of CK2 α by strengthening its interaction with [Pim1](#), whereas glycosylation of Ser347 seems to be antagonistic to Thr344 phosphorylation and permissive to proteasomal degradation. By performing kinase assays with site-specific phospho- and glyco-modified CK2 α in combination with CK2 β and [Pim1](#) binding partners on human protein microarrays, we show that the kinase substrate selectivity of CK2 is modulated by these specific post-translational modifications. This study suggests how a promiscuous protein kinase can be regulated at multiple levels to achieve particular biological outputs.

Figures at a glance



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Poster: The human protein methyltransferases Given their roles in regulating gene expression and driving disease, protein methyltransferases (PMTs) have attracted attention as potential drug targets. Several classes of small-molecule PMT inhibitors have been identified, but new specific chemical probes will be required to elucidate the biological roles of PMTs and serve as leads for PMT-focused drug development.

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Proteins **Genes** Antibodies

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2. Peptidyl-prolyl cis-trans isomerase NIMA-interacting 1 *Homo sapiens*
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4. Cyclin-dependent kinase 1 *Homo sapiens*
5. Casein kinase II subunit alpha *Bos taurus*

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NATURE CHEMISTRY | ARTICLE

A biomimetic polyketide-inspired approach to small-molecule ligand discovery

Claudio Aquino, Mohosin Sarkar, Michael J. Chalmers, Kimberly Mendes, Thomas Kodadek & Glenn C. Micalizio

[Affiliations](#) | [Contributions](#) | [Corresponding authors](#)

Nature Chemistry 4, 99–104 (2012) | doi:10.1038/nchem.1200
Received 21 June 2011 | Accepted 14 October 2011 | Published online 20 November 2011

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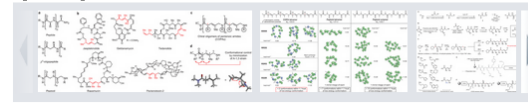
Abstract

[Abstract](#) | [Main](#) | [Results](#) | [Discussion](#) | [References](#) | [Acknowledgements](#) | [Author information](#) | [Supplementary information](#)

The discovery of new compounds for the pharmacological manipulation of protein function often embraces the screening of compound collections, and it is widely recognized that natural products offer beneficial characteristics as protein ligands. Much effort has therefore been focused on 'natural product-like' libraries, yet the synthesis and screening of such libraries is often limited by one or more of the following: modest library sizes and structural diversity, conformational heterogeneity and the costs associated with the substantial infrastructure of modern high-throughput screening centres. Here, we describe the design and execution of an approach to this broad problem by merging principles associated with biologically inspired oligomerization and the structure of polyketide-derived natural products. A novel class of chiral and conformationally constrained oligomers is described (termed 'chiral oligomers of pentenoic amides', COPA), which offers compatibility with split-and-pool methods and can be screened en masse in a batch mode. We demonstrate that a COPA library containing 160,000 compounds is a useful source of novel protein ligands by identifying a non-covalent synthetic ligand to the DNA-binding domain of the p53 transcription factor.

Subject terms: [Chemical biology](#) | [Organic chemistry](#)

Figures at a glance



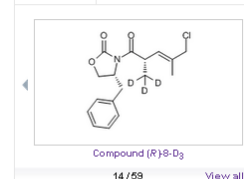
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News and Views

by Aubé
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Results and discussion

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Stereoselective synthesis of the right-hand segment. In the forward direction, the following key operations were proposed: (i) stereoselective construction of the strained four-membered carbon ring by a base-induced intramolecular cyclization reaction of an epoxy nitrile bearing an **indane** skeleton based on the Stork protocol²⁴, leading to the tricyclo[5.2.1.0^{1,6}]decane skeleton (DEF ring system); (ii) one-step synthesis of the ABC carbon framework by an intramolecular Diels–Alder reaction of a key precursor including a furan (diene component) and α,β -unsaturated ketone (dienophile) moieties in the molecule.

Our first objective focused on the stereoselective synthesis of the crucial precursor epoxy nitrile **9** for construction of the tricyclo[5.2.1.0^{1,6}]decane skeleton (DEF ring system). The targeted molecule **9** was a *trans*-fused **indane** derivative synthesis therefore appeared precursor **9**, starting from **1** a protocol recently reported **aluminium trifluoro- methanesulfonate** at the bridge heads; its synthesis of the requisite an optically active form using an **aluminium trifluoro- methanesulfonate** (**Al(OTf)₃**) in **1,2-dichloroethane ((CH₂Cl)₂)**, **trifluoromethanesulfonic acid (mCPBA)** in **dichloromethane (CH₂Cl₂)** provided **p-epoxide** stereoselectively, which, on treatment with **trimethylaluminium (Me₃Al)** in the presence of **aluminium trifluoro- methanesulfonate (Al(OTf)₃)** in **1,2-dichloroethane ((CH₂Cl)₂)**, underwent a Meinwald rearrangement to give keto acetate **5** as a single product. After treatment of the keto acetate with **1,8-diazabicyclo[5.4.0]undec-7-ene (DBU)** in **CH₂Cl₂**, the resulting enone (67% yield, three steps) was subjected to the Grignard reaction with **vinylmagnesium bromide** in the presence of **cerium(III) chloride (CeCl₃)** in **tetrahydrofuran (THF)** to afford allylic alcohol **6** in 96% yield. As expected, addition of the Grignard reagent occurred exclusively from the opposite side of the angular methyl group. Oxidation of the allylic alcohol with **tert-butyl hydroperoxide (TBHP)** in the presence of **titanium(IV) isopropoxide (Ti(OⁱPr)₄)** and molecular sieves **4Å (MS4Å)** in **CH₂Cl₂** afforded α -epoxy alcohol **7** in 92% yield.

PubChem Compound Summary for trifluoromethanesulfonic acid (CID 2737634). The page includes a table of contents, biomedical annotation, and related chemical classification. A chemical structure is shown in 2D and 3D views.

ChemSpider entry for aluminium triflate (2019266). The page shows the chemical structure, associated data sources, and commercial suppliers.

Data Source	External ID(s)
Sigma-Aldrich	515884_ALDRICH
Alfa Aesar	36568, B20785
Apollo Scientific Limited	PC1010
BePharm	B113739
MolPort	MolPort-001-772-128
Santa Cruz Biotechnology	sc-233855
Shanghai IS Chemical Technology	I09-1763

External data/information

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Introduction

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Most major histocompatibility complex (MHC) class I-peptide ligands that can be bound with high affinity are derived from degradation and cytosolic aminopeptidase-mediated trimming of proteasomal antigens, but many epitopes require an additional transporter associated with antigen processing (TAP) for transport into the ER. A TAP-independent, interferon- γ -inducible, metalloaminopeptidase that was termed ER-associated aminopeptidase 1 (ERAP1) or ER aminopeptidase associated with antigen processing (ERAAP)^{4, 5}.

Studies of ERAP1-deficient cells have shown that ERAP1 generates many larger precursors, but it can destroy other epitopes by trimming them below the MHC class I binding⁶. The peptide repertoire carried by MHC molecules of wild-type mice is substantially⁷. Epitope immunodominance hierarchies differ in wild-type mice with LCMV⁸, and T-cell responses against many model antigens were reduced in ERAP1-deficient mice⁹. Furthermore, cross-presentation of cell-associated epitopes was lower in ERAP1-deficient mice¹⁰. ERAP1-dependent epitopes were shown to be important in resistance to *Toxoplasma gondii*¹¹.

Endoplasmic reticulum aminopeptidase 1
ERAP1
Homo sapiens
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Endoplasmic reticulum aminopeptidase 1
Erap1
Mus musculus
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ERAP1 endoplasmic reticulum aminopeptidase 1 [Homo sapiens]
 Gene ID: 51752, updated on 14-May-2011

Summary

Official Symbol ERAP1 provided by HUGO
Official Full Name endoplasmic reticulum aminopeptidase 1 provided by HUGO
Primary source HUGO:18173
Locus tag UNQ584PFC1154
See related Ensembl:ENSG00000164307, HPRD:06015, MIM:606872
Gene type protein coding
RefSeq status REVIEWED
Organism Homo sapiens
Lineage Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi; Mammalia; Eutheria; Euarchontoglires; Primates; Haplorhina; Catarrhini; Hominoidea
Also known as ALAP; A-LAP; ARTS1; ERAP; APPLS; ARTS-1; ERAP1; PILSAP; PILS-AP; KIA0525; ERAP1
Summary The protein encoded by this gene is an aminopeptidase involved in trimming HLA class I-binding precursors so that they can be presented on MHC class I heterodimer with ERAP2. This protein may also be involved in blood pressure regulation by inactivation of angiotensin II. Three transcript variants exist.

Genomic context
 chromosome 5:Location: 5q15

Genomic regions, transcripts, and products

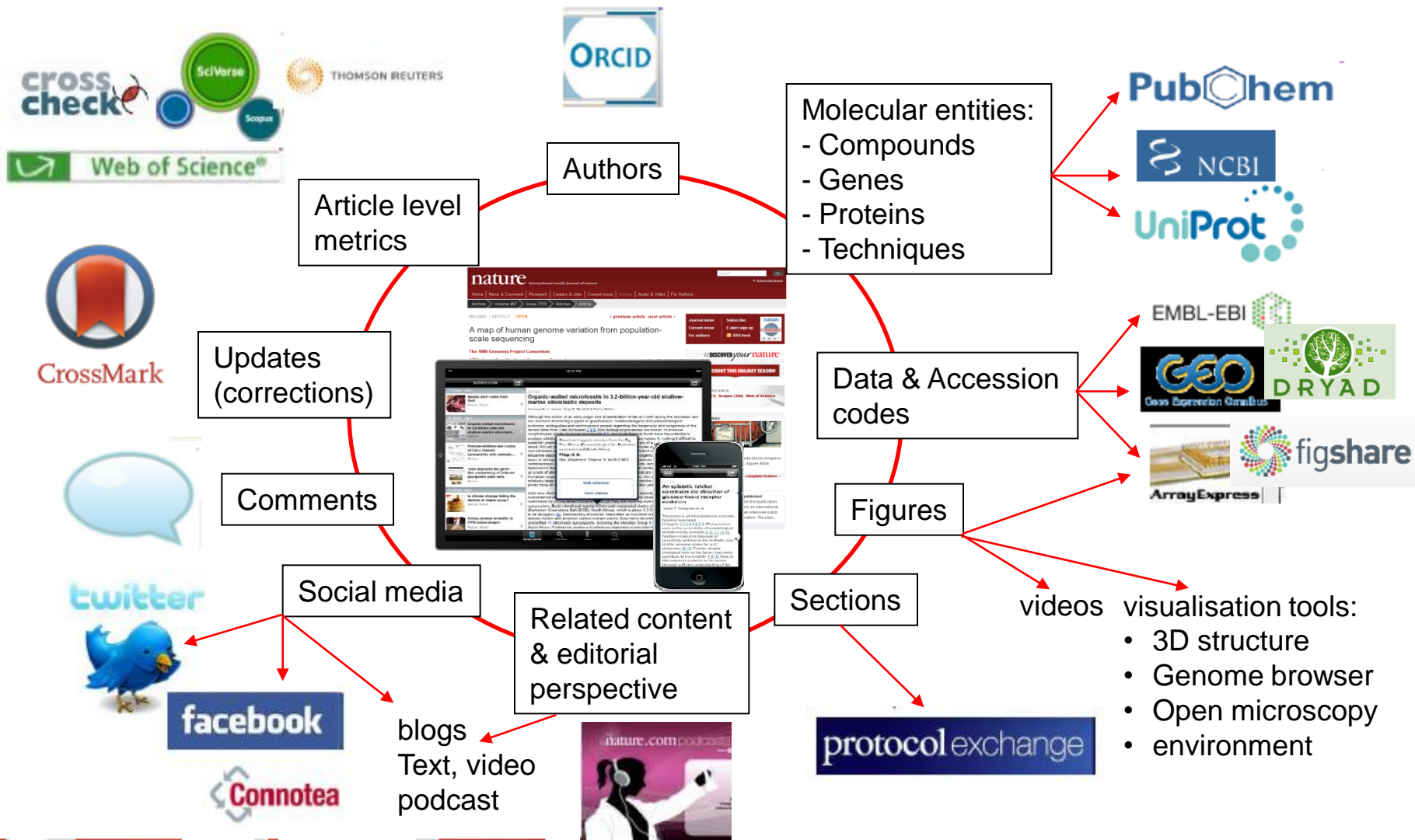
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- Antigen peptide transporter 1**
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A WEEKLY ILLUSTRATED JOURNAL OF SCIENCE

*"To the solid ground
Of Nature trusts the mind which builds for aye."*—WORDSWORTH

THURSDAY, NOVEMBER 4, 1869

NATURE: APHORISMS BY GOETHE

NATURE! We are surrounded and embraced by her: powerless to separate ourselves from her, and powerless to penetrate beyond her.

Without asking, or warning, she snatches us up into her circling dance, and whirls us on until we are tired, and drop from her arms.

She is ever shaping new forms: what is, has never yet been; what has been, comes not again. Everything is new, and yet nought but the old.

We live in her midst and know her not. She is incessantly speaking to us, but betrays not her secret. We constantly act upon her, and yet have no power over her.

The one thing she seems to aim at is Individuality; yet she cares nothing for individuals. She is always building up and destroying; but her workshop is inaccessible.

Her life is in her children; but where is the mother? She is the only artist; working-up the most uniform material into utter opposites; arriving, without a trace of effort, at perfection, at the most exact precision, though always veiled under a certain softness.

Each of her works has an essence of its own; each of her phenomena a special characterisation: and yet their diversity is in unity.

She performs a play; we know not whether she sees it herself, and yet she acts for us, the lookers-on.

Incessant life, development, and movement are in her, but she advances not. She changes for ever and ever, and rests not a moment. Quietude is inconceivable to her, and she has laid her curse upon rest. She is firm. Her steps are measured, her exceptions rare, her laws unchangeable.

She has always thought and always thinks; though not as a man, but as Nature. She broods over an

all-comprehending idea, which no searching can find out.

Mankind dwell in her and she in them. With all men she plays a game for love, and rejoices the more they win. With many, her moves are so hidden, that the game is over before they know it.

That which is most unnatural is still Nature; the stupidest philistinism has a touch of her genius. Whoso cannot see her everywhere, sees her nowhere rightly.

She loves herself, and her innumerable eyes and affections are fixed upon herself. She has divided herself that she may be her own delight. She causes an endless succession of new capacities for enjoyment to spring up, that her insatiable sympathy may be assuaged.

She rejoices in illusion. Whoso destroys it in himself and others, him she punishes with the sternest tyranny. Whoso follows her in faith, him she takes as a child to her bosom.

Her children are numberless. To none is she altogether miserly; but she has her favourites, on whom she squanders much, and for whom she makes great sacrifices. Over greatness she spreads her shield.

She tosses her creatures out of nothingness, and tells them not whence they came, nor whither they go. It is their business to run, she knows the road.

Her mechanism has few springs—but they never wear out, are always active and manifold.

The spectacle of Nature is always new, for she is always renewing the spectators. Life is her most exquisite invention; and death is her expert contrivance to get plenty of life.

She wraps man in darkness, and makes him for ever long for light. She creates him dependent upon the earth, dull and heavy; and yet is always shaking him until he attempts to soar above it.

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Room-temperature solid-state maser

Mark Oxborrow, Jonathan D. Breeze & Neil M. Alford

Affiliation | Contributions | Corresponding authors

Nature 488, 353–356 (16 August 2012) | doi:10.1038/nature11339
Received 30 March 2012 | Accepted 18 June 2012 | Published online

The invention of the laser has resulted in many innovations, and the device has become ubiquitous. However, the maser, which amplifies microwave radiation rather than visible light, has not had as large an impact, despite being instrumental in the laser's birth^{1,2}. The maser's relative obscurity has mainly been due to the inconvenience of the operating conditions needed for its various realizations: atomic³ and free-electron⁴ masers require vacuum chambers and pumping; and solid-state masers⁵, although they excel as low-noise amplifiers⁶ and are occasionally incorporated in ultrastable oscillators^{7,8}, typically require cryogenic refrigeration. Most realizations of masers also require strong magnets, magnetic shielding or both. Overcoming these various obstacles would improve such as more-sensitive chemical assays, more diagnostics (including tomography) based on enhanced magnetic spectrometers⁹ incorporating maser amplifiers and oscillator experimental demonstration of a solid-state maser operating pulsed mode. It works on a laboratory bench, in air, in the terrestrial magnetic field and amplifies at around 1.45 gigahertz. In contrast to the cryogenic ruby maser¹⁰, in our maser the gain medium is an organic mixed molecular crystal, *p*-terphenyl doped with pentacene, the latter being photo-excited by yellow light. The maser's pumping mechanism exploits spin-selective molecular intersystem crossing¹¹ into pentacene's triplet ground state^{11,12}. When configured as an oscillator, the solid-state maser's measured output power of around -10 decibel milliwatts is approximately 100 million times greater than that of an atomic hydrogen maser¹³, which oscillates at a similar frequency (about 1.42 gigahertz). By exploiting the high levels of spin polarization readily generated by intersystem crossing in photo-excited pentacene and other aromatic molecules, this new type of maser seems to be capable of amplifying with a residual noise temperature far below room temperature.

Subject terms: Physics • Applied physics • Engineering • Chemistry • Materials science

Figures at a glance

Subject terms: Physics • Applied physics • Engineering • Chemistry

Figures at a glance

To the best of our knowledge, no one has previously attempted to make a zero-field maser¹⁴ out of an optically pumped crystal of pentacene-doped *p*-terphenyl. Two other novel features of the device we report here are a microwave cavity containing a dielectric ring of sapphire, which supports a high-Q electromagnetic mode (where Q is the mode's quality factor), and a medical laser, designed for the treatment of vascular skin

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A maser with potential
The maser is the microwave-frequency precursor of the now ubiquitous laser — or 'optical maser', as it was once known. But it has had little technological impact compared with the laser, in large part

News & Views
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 - "Trust me - if you gave people at Google free rein to produce TV you'd end up with a lot of bad sci-fi,"

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