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Dan Pollock

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- Ogden Nash



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NATURE CHEMICAL BIOLOGY | ARTICLE

Acetylation regulates Cyclophilin A catalysis, immunosuppression and HIV isomerization

Michael Lammers, Heinz Neumann, Jason W Chin & Leo C James

Affiliations | Contributions | Corresponding authors

Nature Chemical Biology 6, 331–337 (2010) | doi:10.1038/nchembio.342 Received 27 October 2009 | Accepted 14 January 2010 | Published online 04 April 2010

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Abstract

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Cyclophilin A (CypA) is a ubiquitous *cis–trans* prolyl isomerase with key roles in immunity and viral infection. CypA suppresses T-cell activation through cyclosporine complexation and is required for effective HIV-1 replication in host cells. We show that CypA is acetylated in diverse human cell lines and use a synthetically evolved acetyllysyl-tRNA synthetase/tRNA_{CUA} pair to produce recombinant acetylated CypA in *Escherichia coli*. We determined atomic-resolution structures of acetylated CypA and its complexes with cyclosporine and HIV-1 capsid. Acetylation markedly inhibited CypA catalysis of *cis* to *trans* isomerization and stabilized *cis* rather than *trans* forms of the HIV-1 capsid. Furthermore, CypA acetylation antagonized the immunosuppressive effects of cyclosporine by inhibiting the sequential steps of cyclosporine binding and

calcineurin inhibition. Our results reveal that acetylation regulates key functions of CypA in immunity and viral infection and provide a general set of mechanisms by which acetylation modulates interactions to regulate





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Abstract

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Cyclophilin A (CypA) is a ubiquitous cis-trans prolyl isomerase with key roles in immunity and viral infection. CypA suppresses T-cell activation through cyclosporine complexation and is required for effective HIV-1 replication in host cells. We show that CypA is acetylated in diverse human cell lines and use a synthetically evolved acetyllysyl-tRNA synthetase/tRNA_{CUA} pair to produce recombinant acetylated CypA in Escherichia coli. We determined atomicresolution structures of acetylated CypA and its complexes with cyclosporine and HIV-1 capsid. Acetylation markedly inhibited CypA catalysis of cis to trans isomerization and stabilized cis rather than trans forms of the HIV-1 capsid. Furthermore, CypA acetylation antagonized the immunosuppressive effects of cyclosporine by inhibiting the sequential steps of cyclosporine binding and

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Compound 1

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Acetylation regulates Cyclophilin A catalysis, immunosuppression and HIV isomerization Michael Lammers, Heinz Neumann, Jason W Chin & Leo C James Nature Chemical Biology 6, 331–337 (2010) | doi:10.1038/nchembio.342

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ethylethyl)-6,9,18,24-tetrakis(2-methylpropyl)-, (3S,6S,9S,12R,15S,18S,21S,24S,30S,33S)-

"The future ain't what it used to be" -Yogi Berra







line in the Fig. 4a). The different Ti-Mn interfacial magnetic couplings may be influenced by a different Mn e_q orbital reconstruction promoted by the different strain or thick patterns. Measurements of the XLD sign Fig. 5a), and a further description in the Methods section and in Supplementary at room temperature evidence a change occupation of Mn orbitals at the interface 0.5 Manganese out-of-plane eg d(3z2-r2) or 0.0 are occupied in (LMO 17/STO 2) samples thick LMO layers (see Fig. 3b), whereas (LMO 3/STO 2) superlattices, with a mu thinner manganite layer, promote a pref in-plane $e_g d(x^2-y^2)$ orbital occupation 0.3 0.2 0.1 È 0.0 5c). This pattern of orbital occupation determined by epitaxial strain is in agree with previous reports in ultrathin strained films 2 29 and modifies bonding in a wa may help to understand the sign of the





Ti (a, b) and Mn (c, d) XAS and XMCD spectra of the samples (LMO3/STO 2) (magenta lines) and (LMO 17/STO 2) (black lines). The XA spectra have been corrected by the subtraction of a baseline that takes into account a linear increase of the background inside the L2,3 edges, as well as the background out of the L2,3 edge. The red lines are the integrated area of each signal. The orbital and spin moment of each cation can be consulted at the top of each figure. Arrows indicate the values of p, q and r (see Methods).





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Back

Holographic three-dimensional telepresence using large-area photorefractive polymer

BY P.-A. BLANCHE, A. BABLUMIAN, R. VOORAKARANAM, C. CHRISTENSON, W. LIN, T. GU, D. FLORES, P. WANG, W.-Y. HSIEH, M. KATHAPERUMAL, B. RACHWAL, O. SIDDIQUI, J. THOMAS, R. A. NORWOOD, M. YAMAMOTO & N. PEYGHAMBARIAN



Holography is a technique that is used to display objects or scenes in three dimens dimensional (3D) images, or holograms, can be seen with the unassisted eye and a humans see the actual environment surrounding them. The concept of 3D teleprese dynamic hologram depicting a scene occurring in a different location, has attracte interest since it was depicted in the original *Star Wars* film in 1977. However, the computational power to produce realistic computer-generated holograms 1 and the and dynamically updatable holographic recording media 2 have prevented realizat Here we use a holographic stereographic technique 3 and a photorefractive polym recording medium 4 to demonstrate a holographic display that can refresh images 50 Hz nanosecond pulsed laser is used to write the holographic pixels 5. Multicolc images are produced by using angular multiplexing, and the full parallax display e multiplexing. 3D telepresence is demonstrated by taking multiple images from one transmitting the information via Ethernet to another location where the hologram i quasi-real-time dynamic 3D display. Further improvements could bring applicatio prototyping, advertising, updatable 3D maps and entertainment.

3D display technology is attracting much public attention; events include the recer such as Avatar, the 2008 US election-night 'hologram' reporter interviews from C (<u>http://www.cnn.com/2008/TECH/11/06/hologram.yellin/index.html</u>), and the der televisions by some manufacturers (<u>http://www.3dtvsource.com/</u>). As dramatic as

nature.com reader

09:34

NEWS

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Mayans converted wetlands to farmland

BY AMANDA MASCARELLI

The ancient Maya civilization is widely recognized for its awe-inspiring pyramids, sophisticated mathematics and advanced written language. But research is revealing that the complexity of Maya agricultural systems is likely to have rivalled that of their architecture and intellect.

Using new techniques and extensive excavations, researchers have found that the Maya coped with tough environmental conditions by developing ingenious methods to grow crops in wetland areas. "The work shows that this intensive agriculture is more complicated and on a par with these other areas



Maya irrigation canals at "Birds of Paradise" site in northwest Belize. Credit: S. Luzzadder-Beach

of intellectual development," says Timothy Beach, a physical geographer at Georgetown University in Washington DC, who presented his findings on Wednesday at the Geological Society of America (GSA) meeting in Denver, Colorado.

The Maya civilization, considered one of the most advanced ancient societies, lived in sprawling and

Nature News

Mayans converted wetlands...

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FEBRUARY 21, 2011

Why scientists should blog about their pets

Our <u>March issue</u> went live today, featuring a <u>Thesis article</u> (sub req'd) from Michelle Francl about blogging - here's a little extra from Michelle that expands on her column.

.....

Last fall, Royce Murray stirred up science bloggers by characterizing them as unqualified purveyors of pseudoscience in search of easy money. The response was fast and furious - so robust in fact that performing the Google search that Murray referred to in his argument "qualifications of bloggers" now turns up as many hits to science blogs responding to Murray's editorial as it does adverts and advice for the unqualified seeking to blog (at least in the top twenty!).

I argue in my Thesis column this month that chemistry blogs are a critical part of the communication network which supports good research - and that scientists should read, and if they are so inclined write, blogs of this sort.

What I didn't say is that I would extend this to suggest that scientists should be doing more than utilitarian writing. We should move beyond the writing of journal articles, reviews, abstracts, and even blog posts critically commenting on the literature and write about the quotidian challenges of doing science, extol the beauty of our latest compound, wax philosophical about the reality of molecular orbitals, and dare I say it, blog about our pets.

Simply writing more is a strategy to become a faster, fluent and more efficient writer. Why not write summaries of the latest literature? Why do I think writing about <u>the steamboat buffet my student treated me to in Singapore</u> or <u>my cat's</u> <u>latest predatory exploits</u> is worth my time? Because I can write with the brakes off. I can use language wildly, without worrying about transgressing technical boundaries or overreaching my data.

Learning to deploy rich descriptive language takes practice, and has hidden benefits to the research scientist. Scientists' field notes and lab notebooks would benefit from fluent, descriptive writing - and so, in my experience, would the science that flows from them. The original sceptical chemist, Robert Boyle, held that science wasn't officially science unless you'd



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2',7'-dichlorofluorescein (H2DCF) and Dihydroethidium (DHE), have been used extensively in tissue culture experiments to evaluate reactive oxygen species (ROS) production. However, i...



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Academia: The changing face of tenure

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Biologist Rafael Carazo Salas doesn't have tenure — nor is he expecting to pursue the tenure-track system any time soon. As a faculty member at a UK institution, he doesn't have that option — academic tenure per se in the United Kingdom was abolished more than 20 years ago.

But Carazo Salas, a group leader at the University of Cambridge, UK, isn't lying awake at night trying to dream up

Nature

Why so many rare variants?

Shared by NatureNews

blogs.nature.com - Unsurprisingly, this year is about the 1000 Genomes Project, the eagerly awaited pilot data for which was published last week. One of the main take-home messages from the analysis has been the huge number of rare variants the study has turned up so far.

In a talk earlier today, Andy Clark, a population geneticist at Cornell University, gave a tantalizing explanation for why rare variants are so numerous: population size. For millennia, population growth had been fairly static, but over the last couple centuries it has begun to shoot up wildly, with the

FierceBiotech's Top Writers in Biotech I Pharma Marketer

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pharma-marketer.com - Thanks to the web, the biotech scene is teeming with writers with lots of insights to offer on the latest news and trends. With no hometown newspaper for an industry scattered around the globe, and precious few industry pubs worth subscribing to, the Internet has become the go-to place for anyone looking to stay up-to-the-minute on biopharma. Once news breaks it's first tweeted and then analyzed-usually in a matter of minutes. Within a few hours you can get a debate going. By next day, it's on to something Note the different layout between "publications" and within them.

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"Once journal content is opened up to Google for indexing, Google is then used by large numbers of even the most proficient and informed information seekers.

Just four months after ScienceDirect content in physics was opened up to Google, more than a third of all traffic arrived via this route. This is particularly notable in a field richly endowed with online information resources.

- E-journals: their use, value and impact, RIN, April 2009

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Protein Measurement with the Folin Phenol Reagent

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...a method for measuring the amount of protein in solutions. As of January 2004, it was cited 275,669 times

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Tumour-infiltrating regulatory T cells stimulate mammary cancer metastasis through RANKL–RANK signalling. Wei Tan, Weizhou Zhang, Amy Strasner, Sergei Grivennikov, Jin Q. Cheng, Robert M. Hoffman & Michael Karin

Nature 470, 548–553 (24 February 2011) doi:10.1038/nature09707

Fat cells reactivate quiescent neuroblasts via TOR and glial insulin relays in Drosophila. Rita Sousa-Nunes, Lih Ling Yee & Alex P. Gould.

Nature (2011) doi:10.1038/nature09867 [Accessed 26 Feb 2011]

But even then...



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tolic BP [9]

doi:10.1038 /nrcardio.20 10.20

How do we

Key advances

assessed.

• Targeting a systolic BP <120 mmHg, com-

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tion in BP can account for differences in ef-

stroke independently of effects on mean sys-

fects of antihypertensive drugs on risk of

12 of 645

23:24)% Library ≔ Nature Reviews Key Advances in Medicine 2010 $\dot{\otimes}$ A Q pared with <140 mmHg, did not reduce ma-**Hypertension in 2010** jor cardiovascular events in patients with type 2 diabetes at high risk for cardiovascu-New challenges in lar disease [1] · Tight control of systolic BP among patients blood pressure goals with diabetes and coronary artery disease was not associated with improved cardiovasand assessment cular outcomes compared with usual control [2] Suzanne Oparil · Visit-to-visit variability in systolic BP in individual patients is increased in those at high Provocative new studies have shown that tight blood pressure (BP) control (goal sysrisk of stroke, is reproducible, and a powertolic BP <120 mmHg) in high-risk patients ful predictor of stroke independent of mean with diabetes mellitus confers no significant systolic BP [7] cardiovascular benefit other than stroke re- Increased residual variability in systolic BP duction, and that BP variability is important in patients with treated hypertension is ~~ for the diagnosis and management of hyperciated with a high risk of vascular even tension. The impact of these findings on fu-13 of 645 11 pages left in this chapter Drug-class effects on interindividual v ture hypertension guidelines remains to be tion in BP can account for differences assessed. fects of antihypertensive drugs on risk on Key advances stroke independently of effects on mean systolic BP [9] • Targeting a systolic BP <120 mmHg, com-••••• Back to page 558 12 of 645 13 of 645 11 pages left in this chapter Key Advances in Medicine 2010 🔅 ${}_{A}A$ Q ≣ Library Nature Reviews ment of hypertension. The impact of these findings on future hypertension Hypertension in 2010 guidelines remains to be assessed. New challenges in Key advances blood pressure Targeting a systolic BP <120 mmHg, compared with <140 mmHg, did not goals and assessreduce major cardiovascular events in patients with type 2 diabetes at high ment risk for cardiovascular disease [1] 17 of 850 16 pages left in this chapter Tight control of systolic BP among Suzanne Oparil patients with diabetes and coronal Provocative new studies have shown artery disease was not associated with that tight blood pressure (BP) control improved cardiovascular outcomes

(goal systolic BP <120 mmHg) in high-risk patients with diabetes mellitus confers no significant cardiovascular benefit other than stroke reduction, and that BP variability is important for the diagnosis and manage-

•••• Back to page 735

- compared with usual control [2]
- Visit-to-visit variability in systolic BP in individual patients is increased in those at high risk of stroke, is reproducible, and a powerful predictor of

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The single biggest problem in communication is the illusion that it has taken place.

George Bernard Shaw

