The future of the science publishing ego-system

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if there is one

The future of the science publishing ego-system

Ego-system?

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J.J.M. Velterop, “Keeping the Minutes of Science.” In: Electronic library and visual information research (Elvira 2). Edited by Mel Collier and Kathryn Arnold. Proceedings of the second ELVIRA conference, held in May 1995 at De Montfort University, Milton Keynes. Aslib. 1995, pp 11-17.

KEEPING THE MINUTES OF SCIENCE

J. J.M. Velterop
Academic Press Ltd, London, UK

INTRODUCTION

Scientific journal publishing differs markedly from most other kinds of publishing. Born out of the exchange of letters on scientific topics and results, it has evolved into as much a service to scientists who need to publish the results of their work, as a

Changes to the Current Publishing System

- Increasing Open Access — new models
- Separation of Peer Review and Publishing
- Changes to Peer Review — more open
- More arXiv-oids
- “Extrajournaleous” articles
- User-defined formats
- *Et cetera, et cetera*

User-defined Formats

1. Introduction

The problem considered in the following pages is what is sometimes called the problem of 'indefinite integration' or of 'finding a function whose differential coefficient is a given function'. These descriptions are vague and in some ways misleading; and it is necessary to define our problem more precisely before we proceed further [1].

Let us suppose for the moment that $f(x)$ is a real continuous function of the real variable x. We wish to determine a function y whose differential coefficient is $f(x)$, or to solve the equation [2]. It is proved in [3] that the solution blows up in finite time for more general kernels.

$$z_i(\infty) = 0 \quad \text{for } i = 0, 1, \ldots, 2N-1, \tag{1}$$

Let us denote by $P(x, y)$ a polynomial such as occurs on the left-hand side of Eq. (7). Then there are two possibilities as regards any particular polynomial $P(x, y)$. Either it is possible to express $P(x, y)$ as the product of two polynomials of the same type, neither of which is a mere constant, or it is not. In the first case $P(x, y)$ is said to be *reducible*, in the second *irreducible*. Thus second-kind [4] since the exponents α, β cannot rings [3].

$$\begin{aligned} \delta s_1 = -z_2(L), \qquad \delta s_2 \\ = -\left(z_4(L) + \frac{L^2}{14} z_2(L)\right). \end{aligned} \tag{2}$$

Image courtesy of
Kaveh Bazargan

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However

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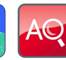

RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

IMPAD1 Mutations in Two Catel-Manzke Like Patients

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Catel–Manzke syndrome is characterized by hyperphalangism with bilateral deviation of the index fingers and micrognathia with or without cleft palate. Some atypical patients present with additional malformations. No molecular basis is yet available. Most patients have an unremarkable family history but autosomal recessive inheritance has been recently suggested in a consanguineous family with recurrence in sibs. Catel–Manzke syndrome has overlapping features with Desbuquois dysplasia type 1 due to *CANT1* (calcium-activated nucleotidase 1) mutations and also with "chondrodysplasia with joint dislocations, gPAPP type" due to *IMPAD1* (Inositol Monophosphatase Domain containing 1) mutations recently reported in four patients, all characterized by short stature, joint dislocations, brachydactyly and cleft palate. The aim of our study was to screen *CANT1* and *IMPAD1* in Catel–Manzke patients. Three patients were diagnosed as classical Catel–Manzke syndrome and two as Catel–Manzke like patients, based on the presence of additional features. We identified two homozygous loss-of-function *IMPAD1* mutations in the two Catel–Manzke like patients (p.Arg187X and p.Ser108ArgfsX48). The phenotype was characterized by severe growth retardation with short and abnormal extremities, cleft palate with micrognathia and knee hyperlaxity. Radiographs of hands and feet revealed numerous accessory bones with abnormally shaped phalanges and carpal synostosis. Based on this report, we concluded that *IMPAD1* should be screened for patients with Catel–Manzke and additional features. © 2012 Wiley Periodicals, Inc.

Key words: autosomal recessive inheritance; Catel–Manzke; cleft palate; *IMPAD1*

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Am J Med Genet Part A 158A:2183–2187.

INTRODUCTION

Catel–Manzke syndrome or palatodigital syndrome Catel–Manzke type [OMIM 302380] is characterized by hyperphalangism and micrognathia [Manzke, 1966]. Some patients present with the full range of Pierre Robin sequence, comprising a combination of micrognathia and glossoptosis with or without cleft palate. Hand X-rays show a bilateral shortening and radial deviation of the index finger due to an accessory bone at the metacarpo-phalangeal joint. To date, 34 patients have been reported in literature [Kapoor et al., 2011; Manzke et al., 2008]. Most of them are sporadic but some familial cases with various relationships (sibs, grandfather–grandchild) have been described and recently autosomal recessive inheritance has been suggested in one consanguineous family with recurrent sibs [Kiper et al., 2011].

There is clinical overlap with the multiple dislocation group (group 20 in the international classification of bone disorders [Warman et al., 2011]), and especially with Desbuquois dysplasia [OMIM 251450] which is characterized by short stature, joint dislocations, hand anomalies, advanced bone age and a "Swedish key" appearance of the proximal femur [Le Merrer et al., 1991]. *CANT1* (calcium-activated nucleotidase 1) mutations have been reported in Desbuquois dysplasia type 1 patients

Additional supporting information may be found in the online version of this article.

The authors declare no conflict of interest.

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Characterization of a new series of non-covalent proteasome inhibitors with exquisite potency and selectivity for the 20S β5-subunit

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Discovery, Millennium Pharmaceuticals, Inc., 40 Landsdowne Street, Cambridge, MA 02139, U.S.A.

The mammalian 26S proteasome is a 2500 kDa multi-catalytic complex involved in intracellular protein degradation. We describe the synthesis and properties of a novel series of non-covalent di-peptide inhibitors of the proteasome used on a capped tri-peptide that was first identified by high-throughput screening of a library of approx. 350000 compounds for inhibitors of the ubiquitin–proteasome system in cells. We show that these compounds are entirely selective for the β5 (chymotrypsin-like) site over the β1 (caspase-like) and β2 (trypsin-like) sites of the 20S core particle of the proteasome, and over a panel of less closely related proteases. Compound optimization, guided by X-ray crystallography of the liganded 20S core particle, confirmed their non-covalent binding mode and provided a structural basis for their enhanced *in vitro* and cellular potencies. We demonstrate that such compounds show low nanomolar IC_{50} values for the human 20S β5 site *in vitro*, and that pharmacological inhibition of this site in cells is sufficient to potently inhibit the degradation of a tetra-ubiquitin–luciferase reporter, activation of NFκB (nuclear factor κB) in response to TNF-α (tumour necrosis factor-α) and the proliferation of cancer cells. Finally, we identified capped di-peptides that show differential selectivity for the β5 site of the constitutively expressed proteasome and immunoproteasome *in vitro* and in B-cell lymphomas. Collectively, these studies describe the synthesis, activity and binding mode of a new series of non-covalent proteasome inhibitors with unprecedented potency and selectivity for the β5 site, and which can discriminate between the constitutive proteasome and immunoproteasome *in vitro* and in cells.

Key words: chymotrypsin-like, immunoproteasome, 26S proteasome, proteasome inhibitor, β5-subunit, ubiquitin–proteasome system (UPS).

INTRODUCTION

The 26S proteasome is a very large (2500 kDa) multi-subunit proteolytic complex found in high abundance in all eukaryotic cells that is responsible for the regulated degradation of the majority of intracellular proteins, including those involved in signal transduction, cell-cycle control, apoptosis and inflammatory responses [1–6]. It is composed of the 20S catalytic core particle that is capped at one or both ends by the 19S regulatory complex, also called PA700 [1–6]. The 20S core particle is comprises four stacked heteroheptameric rings that form a cylindrical structure with 2-fold axial symmetry. The two outer α rings gate substrate entry through their interaction with the 19S regulatory complex, which itself serves to bind, unfold, de-ubiquitinate and translocate into the catalytic core substrate proteins that have been conjugated to poly-ubiquitin [1–6]. The two inner β rings form the central proteolytic chamber and each contain three active sites with distinct substrate specificities. These are located on the β1, β2 and β5 subunits and are referred to as having caspase-like, trypsin-like and chymotrypsin-like activities on the basis of their preference for cleaving peptides after acidic, basic or hydrophobic amino acid residues respectively [1–6]. A second form of the 20S proteasome termed the immunoproteasome exists in cells of lymphoid origin and can be induced in most, if not all, cells in response to the pro-inflammatory cytokine interferon-γ [5–7]. This enzyme contains distinct catalytic subunits, designated β1i, β2i and β5i, and is primarily involved in the generation of antigenic peptides for MHC class I presentation, although a function for the immunoproteasome in cytokine production has also been described [8].

For each of the 20S catalytic β-subunits, the hydroxy group of the N-terminal threonine residue ($Thr^{1O\gamma}$) serves as the nucleophile that initiates cleavage of the peptide bond [4,5,9]. Various natural and synthetic compounds that contain electrophilic centres or 'warheads' inhibit the proteasome by forming covalent adducts with these active-site threonine residues, including peptide aldehydes, vinyl sulfones, boronic acids, α′β′-epoxyketones, 2-keto-1,3,4-oxadiazoles and β-lactones (Figure 1A) [4–6,9–11]. The di-peptide boronic acid bortezomib (PS-341 or VELCADE®, Millennium Pharmaceuticals, Inc.) is among the most potent, stable and selective of these inhibitors [12–15], and shows nanomolar potency with respect to cytotoxicity across a broad range of human tumour cell types *in vitro* [13,14]. It is in clinical use for the treatment of multiple myeloma [16–19] and refractory mantle cell lymphoma [20],

Abbreviations used: Ac, acetyl; AMC, 7-amino-4-methylcoumarin; Boc, t-butoxycarbonyl; HBTU, *O*-benzotriazole-*N,N,N′,N′*-tetramethyluronium hexafluorophosphate; HEK, human embryonic kidney; LC_{50}, half-maximal lethal concentration; MPD, 2-methyl-2,4-pentanediol; NFκB, nuclear factor κB; IκB, inhibitory protein of NFκB; NFκB-Luc, NFκB–luciferase; PA, proteasomal activator; PDL, poly-D-lysine; RNAi, RNA interference; siRNA, small interfering RNA; Suc, succinyl; TEV, tobacco etch virus; TNF-α, tumour necrosis factor-α; 4xUb-Luc, tetra-ubiquitin–luciferase; UPS, ubiquitin–proteasome system; Z, benzyloxycarbonyl.

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The structural co-ordinates of the yeast 20S proteasome with the indicated ligand bound reported will appear in the PDB under accession codes: 3MG0 (bortezomib); 3MG4 (compound 1); 3MG6 (compound 6); 3MG7 (compound 8); 3MG8 (compound 16).

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Biochemical Journal

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RESEARCH ARTICLE

A bacterial sulfonolipid triggers multicellular development in the closest living relatives of animals

Rosanna A Alegado[1†], Laura W Brown[2†], Shugeng Cao[2], Renee K Dermenjian[2], Richard Zuzow[3], Stephen R Fairclough[1], Jon Clardy[2*], Nicole King[1*]

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Abstract Bacterially-produced small molecules exert profound influences on animal health, morphogenesis, and evolution through poorly understood mechanisms. In one of the closest living relatives of animals, the choanoflagellate *Salpingoeca rosetta*, we find that rosette colony development is induced by the prey bacterium *Algoriphagus machipongonensis* and its close relatives in the Bacteroidetes phylum. Here we show that a rosette inducing factor (RIF-1) produced by *A. machipongonensis* belongs to the small class of sulfonolipids, obscure relatives of the better known sphingolipids that play important roles in signal transmission in plants, animals, and fungi. RIF-1 has extraordinary potency (femtomolar, or 10^{-15} M) and *S. rosetta* can respond to it over a broad dynamic range—nine orders of magnitude. This study provides a prototypical example of bacterial sulfonolipids triggering eukaryotic morphogenesis and suggests molecular mechanisms through which bacteria may have contributed to the evolution of animals.
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Introduction

Eukaryotes evolved in a world filled with bacteria and throughout their shared history these two branches of life have developed a complex set of ways to compete and cooperate with each other. While research on these interactions has historically emphasized bacterial pathogens, bacteria also regulate the biology of eukaryotes in many other ways (***McFall-Ngai 1999***; ***Koropatnick et al. 2004***; ***Mazmanian et al. 2005***; ***Falkow 2006***; ***Hughes and Sperandio 2008***; ***Desbrosses and Stougaard 2011***) and may have exerted critical influences on animal evolution. Choanoflagellates, microscopic bacteria-eating eukaryotes that are the closest living relatives of animals (***James-Clark 1868***; ***Saville Kent 1880***; ***Hibberd 1975***; ***Carr et al. 2008***; ***King et al. 2008***; ***Ruiz-Trillo et al. 2008***), could provide particularly important insights into the mechanisms underlying bacterial influences on animal biology and evolution. Moreover, some choanoflagellates have both solitary and multicellular stages in their life histories (***Leadbeater 1983***; ***Karpov and Coupe 1998***; ***Dayel et al. 2011***) and understanding the environmental cues that regulate choanoflagellate colony formation could provide a molecular model for animal multicellularity.

Results

In the choanoflagellate *Salpingoeca rosetta*, rosette-shaped multicellular colonies develop when a single founder cell undergoes multiple rounds of incomplete cytokinesis, leaving neighboring cells physically attached by fine intercellular bridges (***Fairclough et al. 2010***; ***Dayel et al. 2011***). Although the original stock of *S. rosetta* (ATCC50818) was established from a rosette colony (***Dayel et al.***

The *Mycobacterium tuberculosis* Drugome and Its Polypharmacological Implications

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Abstract

We report a computational approach that integrates structural bioinformatics, molecular modelling and systems biology to construct a drug-target network on a structural proteome-wide scale. The approach has been applied to the genome of *Mycobacterium tuberculosis (M.tb)*, the causative agent of one of today's most widely spread infectious diseases. The resulting drug-target interaction network for all structurally characterized approved drugs bound to putative *M.tb* receptors, we refer to as the 'TB-drugome'. The TB-drugome reveals that approximately one-third of the drugs examined have the potential to be repositioned to treat tuberculosis and that many currently unexploited *M.tb* receptors may be chemically druggable and could serve as novel anti-tubercular targets. Furthermore, a detailed analysis of the TB-drugome has shed new light on the controversial issues surrounding drug-target networks [1–3]. Indeed, our results support the idea that drug-target networks are inherently modular, and further that any observed randomness is mainly caused by biased target coverage. The TB-drugome (http://funsite.sdsc.edu/drugome/TB) has the potential to be a valuable resource in the development of safe and efficient anti-tubercular drugs. More generally the methodology may be applied to other pathogens of interest with results improving as more of their structural proteomes are determined through the continued efforts of structural biology/genomics.

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Introduction

The construction and analysis of molecular interaction networks provides a powerful means to understand the complexity of biological systems and to reveal hidden relationships between drugs, genes, proteins, and diseases. In particular, the study of drug-target networks may facilitate an improved understanding of the principles of polypharmacology and hence improved rational drug design [2]. In recent years, several computational methodologies have been developed to predict drug-target networks based on ligand chemistry [4–6], phenotypic changes resulting from drug perturbation [7–9], or a combination of chemical features of drugs and sequence features of protein targets [10–12]. Extensive experimental and computational evaluation has proven that these methods are valuable for drug repurposing and side effect prediction. However, these methods are biased towards known drug-target pairs, which are mainly derived from well-established human target classes such as G-protein coupled receptors (GPCRs), which only cover a small portion of the human proteome. The lack of a broad spectrum of drug-target pairs is more severe in pathogens than it is in human. For example, amongst the 3,999 proteins encoded by the *Mycobacterium tuberculosis* (*M.tb*) genome, only nine (cmaA1, cyp51, embA, embB, embC, folK, InhA, katG and rpoC) have been pharmaceutically investigated [13]. Thus, drug-target networks that are constructed from only existing drug targets are retrospective, and less capable of discovering new druggable targets and predicting off-target profiles of new compounds on a proteome-wide scale. In addition, the incompleteness of drug-target data poses questions as to whether or not the topology of drug-target networks is inherently modular or random [1].

It is important to construct and analyze a proteome-wide drug-target network that includes not only the primary targets, but also all of the potential off-targets of the drugs in the network. Such a network, if available, would provide unparalleled opportunities for mapping a comprehensive drug-target space and understanding the molecular basis of drug efficacy, side- effects and drug resistance, thereby providing the foundation for the rational design of polypharmacological (multi-target) drugs. For anti-infectious drug discovery, where pharmaceutically investigated targets only represent a small portion of the whole pathogen's proteome, it is more challenging to establish a proteome-wide drug-target network. The linkage of drugs to less exploited proteins such as virulence factors, transport proteins and transcription factors will greatly expand the repository of anti-infectious drug targets and provide new solutions for combating multi-drug and extensively drug resistant pathogens, and for repurposing existing drugs for new uses.

Structural bioinformatics provides an alternative and complementary way to extend drug-target networks to less characterized proteins on a proteome-wide scale. The structural coverage of a given pathogen proteome is usually much larger than the

Hydrogen bonding patterns in a series of 1-arylcycloalkanecarboxamides†

Andreas Lemmerer and Joseph P. Michael*

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Single-crystal structures of five 1-arylcycloalkanecarboxamides, *viz.* 1-phenylcyclopentanecarboxamide (**1**), 1-phenylcyclohexanecarboxamide (**2**), 1-(2-fluorophenyl)cyclohexanecarboxamide (**3**), 1-(2-chlorophenyl)cyclohexanecarboxamide (**4**) and 1-(2-bromophenyl)-cyclohexanecarboxamide (**5**), are reported. The primary hydrogen-bonded motif consists of centrosymmetric or non-centrosymmetric $R^2_2(8)$ dimers between the carboxamide functional groups. In compound **1**, the dimers are further linked by hydrogen bonds to form infinite two-dimensional sheets, while in **4** and **5** additional hydrogen bonding with molecules not involved in dimer formation links the dimers into infinite chains. The cycloalkane rings in the five compounds adopt noticeably different conformations. As a consequence of these various effects, none of the five compounds is isostructural.

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Introduction

The rapidly growing discipline of crystal engineering is predicated on molecular recognition between discrete molecules, which permits them to assemble in highly ordered supramolecular arrays by capitalising on various intermolecular interactions.[1,2] Dominant among such molecular interactions is hydrogen bonding, which is frequently the over-riding factor in the design of supramolecular assemblages.[3] As a constituent of 'supramolecular synthons'[2]—the building blocks from which solid-state superstructures are generated—the amide functional group has few equals for the versatility with which it can engage in hydrogen bonding to create a diverse range of packing arrangements.[4,5] Notable is the effect that subtle variations in molecular structure or in the substituents can have on the packing of homomeric hydrogen-bonded amide aggregates.[6] Changes in packing motifs resulting from small variations in molecular structure or substituents have also been observed with other compounds capable of homomeric hydrogen bonding (for example, carboxylic acids,[7] oximes[8] and secondary enaminones[9]), as well as in many heteromeric hydrogen-bonded structures (for example, bisphenol–amine co-crystals).[10]

Our interest in the title compounds originated from synthetic investigations first performed in the 1980s, when we prepared several 1-(2-halophenyl)cyclohexanecarboxamides as part of a model study to identify suitable precursors for the construction of oxindoles bearing spirocyclic rings at C-3.[11,12] These spiro-oxindoles in turn served as models for developing methodology aimed at the total synthesis of the complex spiro-oxindole alkaloid gelsemine.[13] Related 1-phenylcycloalkanecarboxamides have been tested for neuroprotective activity.[14] In this article we report a range of distinctly different hydrogen bonding patterns in five representatives of the title compound, **1–5** (Scheme 1), as revealed by single-crystal X-ray diffraction studies.

Results and discussion

Crystallographic descriptions of the structures of 1-arylcycloalkanecarboxamides 1–5

Table 1 provides crystallographic details for compounds **1–5**. The atomic numbering scheme for all five compounds is given in Fig. 1, which also shows the contents of the asymmetric unit in each case. The distances and angles within the five compounds reported are generally as expected.[15] In all five structures, hydrogen bonds (summarised in Table 2) play a major part in controlling the supramolecular assembly of the molecules. In describing the hydrogen-bonding patterns in the five carboxamide structures reported in this study, we shall use unitary (N_1) and binary (N_2) graph set (GS) analysis.[16] All structures have simple N–H···O hydrogen bonds; and, as expected, the primary hydrogen-bonded motif between molecules (Scheme 1) is a cyclic dimer [Synthon 1, $R^2_2(8)$]. In distinguishing between the two H atoms on the primary amide group, we shall follow the procedure of Desiraju[5] in labelling the N–H atom *syn* to the carbonyl group (*i.e.*, the N–H atom involved in the formation of the cyclic dimer) as 'H_s' and the

1 R = H; *n* = 0
2 R = H; *n* = 1
3 R = F; *n* = 1
4 R = Cl; *n* = 1
5 R = Br; *n* = 1

Scheme 1 Structures of compounds **1–5**, showing the primary hydrogen-bonded dimeric motif.

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† CCDC reference numbers 649368–649372. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b708333e

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Broad-Spectrum Antiviral Therapeutics

Todd H. Rider*, Christina E. Zook, Tara L. Boettcher, Scott T. Wick, Jennifer S. Pancoast, Benjamin D. Zusman

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Abstract

Currently there are relatively few antiviral therapeutics, and most which do exist are highly pathogen-specific or have other disadvantages. We have developed a new broad-spectrum antiviral approach, dubbed Double-stranded RNA (dsRNA) Activated Caspase Oligomerizer (DRACO) that selectively induces apoptosis in cells containing viral dsRNA, rapidly killing infected cells without harming uninfected cells. We have created DRACOs and shown that they are nontoxic in 11 mammalian cell types and effective against 15 different viruses, including dengue flavivirus, Amapari and Tacaribe arenaviruses, Guama bunyavirus, and H1N1 influenza. We have also demonstrated that DRACOs can rescue mice challenged with H1N1 influenza. DRACOs have the potential to be effective therapeutics or prophylactics for numerous clinical and priority viruses, due to the broad-spectrum sensitivity of the dsRNA detection domain, the potent activity of the apoptosis induction domain, and the novel direct linkage between the two which viruses have never encountered.

Citation: Rider TH, Zook CE, Boettcher TL, Wick ST, Pancoast JS, et al. (2011) Broad-Spectrum Antiviral Therapeutics. PLoS ONE 6(7): e22572. doi:10.1371/journal.pone.0022572

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Competing Interests: THR is the inventor on patents and patent applications covering DRACOs: Rider TH (issued October 24, 2006) Anti-pathogen treatments. U.S. Patent 7,125,839; Rider TH (issued July 28, 2009) Anti-pathogen treatments. U.S. Patent 7,566,694; Rider TH (filed June 18, 2009) Anti-Pathogen Treatments. U.S. Patent Application 20100098680; Rider TH (filed February 7, 2003) Anti-Pathogen Treatments. European Patent Application 03716001.7; Rider TH (filed February 7, 2003) Anti-Pathogen Treatments. Canadian Patent Application 2,475,247; Rider TH (filed February 7, 2003) Anti-Pathogen Treatments. Patent Cooperation Treaty Serial No. US03/03978; Rider TH (filed February 7, 2003) Anti-Pathogen Treatments. Japanese Patent Application 2003565429; Rider TH (filed November 19, 2009) Anti-Pathogen Treatments. Japanese Patent Application 2009262426. This does not alter the authors' adherence to all the PLoS ONE policies on sharing data and materials.

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Introduction

A serious threat is posed by viral pathogens, including clinical viruses (HIV, hepatitis viruses, etc.), natural emerging viruses (avian and swine influenza strains, SARS, etc.), and viruses relevant to potential bioterrorism (Ebola, smallpox, etc.). Unfortunately, there are relatively few prophylactics or therapeutics for these viruses, and most which do exist can be divided into three broad categories [1–3]: (1) Specific inhibitors of a virus-associated target (e.g., HIV protease inhibitors, RNAi) generally must be developed for each virus or viral strain, are prone to resistance if a virus mutates the drug target, are not immediately available for emerging or engineered viral threats, and can have unforeseen adverse effects. (2) Vaccines also require a new vaccine to be developed for each virus or viral strain, must be administered before or in some cases soon after exposure to be effective, are not immediately available for emerging or engineered viral threats, can have unforeseen adverse effects, and are difficult to produce for certain pathogens (e.g., HIV). (3) Interferons and other pro- or anti-inflammatories are less virus-specific, but still are only useful against certain viruses, and they can have serious adverse effects through their interactions with the immune and endocrine systems.

To overcome these shortcomings of existing approaches, we have developed and demonstrated a novel antiviral approach that is effective against a very broad spectrum of viruses, nontoxic *in vitro* and *in vivo*, and potentially suitable for either prophylactic or therapeutic administration. Our approach, which we call a **D**ouble-stranded **R**NA (dsRNA) **A**ctivated **C**aspase **O**ligomerizer (**DRACO**), is designed to selectively and rapidly kill virus-infected cells while not harming uninfected cells.

Our DRACO approach combines two natural cellular processes. The first process involves dsRNA detection in the interferon pathway. Most viruses have double- or single-stranded RNA (ssRNA) genomes and produce long dsRNA helices during transcription and replication; the remainder of viruses have DNA genomes and typically produce long dsRNA via symmetrical transcription [4–5]. In contrast, uninfected mammalian cells generally do not produce long dsRNA (greater than ~21–23 base pairs) [4–5]. Natural cellular defenses exploit this difference in order to detect and to attempt to counter viral infections [6–7]. For example, protein kinase R (PKR) contains an N-terminal domain with two dsRNA binding motifs (dsRBM 1 and 2) and a C-terminal kinase domain [8–9]. Binding of multiple PKR proteins to dsRNA with a length of at least 30–50 base pairs [5] activates the PKRs via trans-autophosphorylation; activated PKR then phosphorylates eIF-2α, thereby inhibiting translation of viral (and cellular) proteins. Other examples of proteins that detect viral dsRNA include 2′,5′-oligoadenylate (2–5A) synthetases [10], RNase L (activated via dimerization by 2–5A produced by 2–5A synthetases in response to

Genes to Cells

REVIEW

Genome editing in induced pluripotent stem cells

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The discovery of induced pluripotent stem (iPS) cells has broadened the promises of regenerative medicine through the generation of syngeneic replacement cells or tissues via the differentiation of patient-specific iPS cells. To apply iPS cell-mediated therapy to patients with genetic disorders, however, genome-editing technologies with high efficiency and specificity are needed. Recently, several targeted genome-editing strategies mediated by zinc finger nuclease and transcription activator-like effector nuclease have been applied to human and mouse iPS cells. Furthermore, spontaneous homologous recombination can restore genotype to wild type in mouse iPS cells heterozygous for genetic mutations. Through genome editing, the clinical application of patient-specific genetic mutation-free iPS cells to genetic disorders can finally be realized.

Introduction

Stem cells can be classified as somatic or pluripotent depending on their developmental potential. Somatic stem cells, which have the ability to self-renew and generate limited kinds of somatic cells, function in maintaining homeostasis of the adult body, whereas pluripotent stem cells have a robust ability to self-renew and can differentiate into all cell types in the adult body (Jaenisch & Young 2008; Evans 2011). Several kinds of pluripotent stem cell lines have been established from different cell sources of developing mouse embryos. The mouse embryonic stem (ES) cell is one kind of pluripotent cell, which is isolated from the inner cell mass cells of blastocysts (Evans & Kaufman 1981). ES cells that maintain a normal karyotype are capable of contributing to the normal development of chimeric mice when microinjected into the blastocoel cavity of blastocysts. Furthermore, a robust potential for cell proliferation *in vitro* has resulted in the isolation of individual cell colonies, in which rare genetic modifications are introduced into the genome by homologous and nonhomologous gene integration (Capecchi 1989). The generation of genetically mutated mice has greatly contributed to our understanding of gene function *in vivo*.

The successful generation of human ES cells from blastocysts (Thomson *et al.* 1998) has significantly advanced the field of regenerative medicine, which involves replacing damaged tissue with stem cell–derived tissue, and paved the way for new therapeutic strategies. However, the generation of ES cells from human embryos has raised ethical concerns (Lo & Parham 2009). To circumvent these, other strategies have been used to obtain pluripotent stem cells. Nuclear reprogramming of somatic cells into pluripotential stem cells has been achieved by the transplantation of somatic nuclei into unfertilized eggs (Wilmut *et al.* 1997) and cell fusion between mouse ES cells and somatic cells (Tada *et al.* 2001). Direct reprogramming of somatic cells into induced pluripotent stem (iPS) cells retaining an identity similar to ES cells was achieved by the transient over-expression of defined transcription factors in mice (Takahashi & Yamanaka 2006) and humans (Takahashi *et al.* 2007; Yu *et al.* 2007). Besides ethical issues, human iPS cells have key advantages over human ES cells in generating immuno-rejection-free iPS cell derivatives,

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Genetic Signatures of Exceptional Longevity in Humans

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Abstract

Like most complex phenotypes, exceptional longevity is thought to reflect a combined influence of environmental (e.g., lifestyle choices, where we live) and genetic factors. To explore the genetic contribution, we undertook a genome-wide association study of exceptional longevity in 801 centenarians (median age at death 104 years) and 914 genetically matched healthy controls. Using these data, we built a genetic model that includes 281 single nucleotide polymorphisms (SNPs) and discriminated between cases and controls of the discovery set with 89% sensitivity and specificity, and with 58% specificity and 60% sensitivity in an independent cohort of 341 controls and 253 genetically matched nonagenarians and centenarians (median age 100 years). Consistent with the hypothesis that the genetic contribution is largest with the oldest ages, the sensitivity of the model increased in the independent cohort with older and older ages (71% to classify subjects with an age at death>102 and 85% to classify subjects with an age at death>105). For further validation, we applied the model to an additional, unmatched 60 centenarians (median age 107 years) resulting in 78% sensitivity, and 2863 unmatched controls with 61% specificity. The 281 SNPs include the SNP rs2075650 in *TOMM40/APOE* that reached irrefutable genome wide significance (posterior probability of association = 1) and replicated in the independent cohort. Removal of this SNP from the model reduced the accuracy by only 1%. Further in-silico analysis suggests that 90% of centenarians can be grouped into clusters characterized by different "genetic signatures" of varying predictive values for exceptional longevity. The correlation between 3 signatures and 3 different life spans was replicated in the combined replication sets. The different signatures may help dissect this complex phenotype into sub-phenotypes of exceptional longevity.

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Competing Interests: In the study the authors included 254 subjects enrolled at ELIXIR. There are no patents, products in development or marketed products to declare. This does not alter the authors' adherence to all the PLoS ONE policies on sharing data and materials.

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Introduction

The average human lifespan in developed countries now ranges from about 80 to 85 years. Environmental factors such as lifestyle choices and where we choose to live as well as genetic factors all contribute to healthy aging. Supporting the importance of environmental factors in survival to old age is the 88 year average life expectancy of Seventh-Day Adventists [1], who by virtue of their religion have health related behaviors conducive to healthy aging.

Human twin studies suggest that only 20–30% of the variation in survival to about 85 years is determined by genetic variation [2]. However, the existence of rare families demonstrating remarkable clustering for extreme ages [3,4], the increased relative risks of survival amongst siblings of nonagenarians [5] and of centenarians [6,7,8,9,10,11,12,13], the fact that children of centenarians experience a marked delay in age-related diseases [14], and the similarity of centenarians' lifestyles to the general population [15], all argue that genetic factors play a much stronger role in living 25–35 years beyond the mid-eighties [10,16,17]. Impressively, siblings of centenarians born in 1900 have a relative risk of living nearly 100 years that is 8 (females) to 17 times (males) greater than that for the average of their birth cohort [10]. The rarity of the trait —only 1 centenarian amongst approximately 5,000 people in the US and only 1 supercentenarian (age 110+ years) amongst seven million people [18]— places exceptional longevity in a very different category from both average life expectancy and common complex traits associated with aging.

Based upon the hypothesis that exceptionally old individuals are carriers of multiple genetic variants that influence human lifespan, we conducted a genome-wide association study (GWAS) of centenarians. We began with a traditional one SNP at a time analysis to identify SNPs that are individually associated with exceptional longevity. We then used a novel approach to build a

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REVIEW

Biology of the Mi-2/NuRD Complex in SLAC (Stemness, Longevity/Ageing, and Cancer)

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Abstract: The dynamic chromatin activities of Mi-2/Nucleosome Remodeling and Histone deacetylation (Mi-2/NuRD) complexes in mammals are at the basis of current research on stemness, longevity/ageing, and cancer (4-2-1/SLAC), and have been widely studied over the past decade in mammals and the elegant model organism, *Caenorhabditis elegans*. Interestingly, a common emergent theme from these studies is that of distinct coregulator-recruited Mi-2/NuRD complexes largely orchestrating the 4-2-1/SLAC within a unique paradigm by maintaining genome stability via DNA repair and controlling three types of transcriptional programs in concert in a number of cellular, tissue, and organism contexts. Thus, the core Mi-2/NuRD complex plays a central role in 4-2-1/SLAC. The plasticity and robustness of 4-2-1/SLAC can be interpreted as modulation of specific coregulator(s) within cell-specific, tissue-specific, stage-specific, or organism-specific niches during stress induction, ie, a functional module and its networking, thereby conferring differential responses to different environmental cues. According to "Occam's razor", a simple theory is preferable to a complex one, so this simplified notion might be useful for exploring 4-2-1/SLAC with a holistic view. This thought could also be valuable in forming strategies for future research, and could open up avenues for cancer prevention and antiageing strategies.

Keywords: stemness, longevity, ageing, cancer, 4-2-1/SLAC, Mi-2/NuRD, mammals, *Caenorhabditis elegans*

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Ceci n'est pas un hamburger: modelling and representing the scholarly article

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ABSTRACT. Current approaches to publishing scholarly work are falling behind the growing demands of modern readers, who need easy access to the underlying data, as well as the ability to consume content on an ever-growing variety of electronic devices. The pros and cons of the various formats for representing the scholarly article are hotly contested, but as yet these debates have had little tangible impact on the publishing world where, in spite of its apparent limitations, the PDF remains the dominant form of distribution. We discuss fundamental philosophical differences between a scholarly work and its representation, and describe Utopia Documents, which realizes those differences in software, aiming to resolve many of the current issues in this area.

S. Pettifer

P. McDermott

J. Marsh

D. Thorne

A. Villeger

T.K. Attwood

Introduction

In 1928, Belgian surrealist René Magritte created a painting of a classic tobacco pipe. Under the pipe, in cursive script, is written, 'Ceci n'est pas une pipe' (Figure 1, see p. 209). In this simple picture, which he called *The Treachery of Images*, he attempted to capture the paradox inherent in the distinction between an object and its representation: this was not a pipe, but rather, a depiction of a pipe. Perhaps unexpectedly, the issue of distinguishing between objects and their representations lies at the heart of some of the major issues that challenge scholarly publishing today, with far-reaching consequences for publishing innovations of the future.

In this article, we discuss some of the most fundamental of these challenges. In particular, we take a fresh look at the role of the PDF in mediating between objects and their representations, and introduce a new technology that bridges the gap between research data and our scholarly commentaries on those data. Although the issues we discuss are relevant across the publishing spectrum, we begin in a field where the problems are particularly acute, by considering the current status of scientific data collection and how this relates to the biomedical literature.

A big bang

Different fields of science have followed rather different evolutionary trajectories, reflecting, to some extent, rather different philosophical approaches towards understanding the world around us. Crudely speaking, physicists are used to collecting vast quantities of atomic or subatomic data, and analysing them with respect to largely predictable, universal laws. In its attempts (amongst other things) to shed light on the origins of our universe, for example, CERN's

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On the impossibility of being expert

More scientific papers are being published than ever before. **Alan G Fraser** and **Frank D Dunstan** call for that new strategies to deal with this avalanche of information

Every doctor has an ethical duty to keep up to date. Is this just getting more difficult or has it already become impossible? Since Alvin Toffler coined the phrase "information overload" in 1970,[1] the growth of scientific and medical information has been inexorable. There are now 25 400 journals in science, technology, and medicine, and their number is increasing by 3.5% a year[2]; in 2009, they published 1.5 million articles.[2] PubMed now cites more than 20 million papers.

One response of the medical profession to the increasing scientific basis and clinical capacity of medicine has been to increase subspecialisation. This may restrict the breadth of knowledge of the ultraspecialist, but can such subspecialists maintain their depth of expertise? Taking one medical subspecialty as an example, we have examined the gap between information and human capacity, and we explore the implications for any doctor who wants to practise evidence based medicine.

Methods

We searched the database of the US National Library of Medicine (PubMed) on 12 September 2010 for references relating to diagnostic imaging in cardiology. The table shows the search terms used.

Citations with any reference to echocardiography (the mainstay of diagnosis) were searched first, and then the strategy was narrowed to echocardiography as a main topic and restricted to controlled clinical trials (strategies 1-4; table). It is recommended that junior colleagues should be trained in several imaging modalities,[3] and so we performed further searches for the concept of "multimodality imaging" in cardiology. This included single photon emission computed tomography (SPECT), positron emission tomography (PET), magnetic resonance imaging, computed tomography (CT), and coronary arteriography, as well as cardiovascular ultrasound (strategies 5-6, table).

All searches were performed for each year from 1966 (the year before ultrasonics was introduced as a search term in PubMed; echocardiography was added in 1973) to 2009. Trends in papers on echocardiography were modelled; a good fit—from a cubic model containing time, the square of time, and the cube of time—was used to predict the numbers of publications to the end of 2010 and annually to 2015.

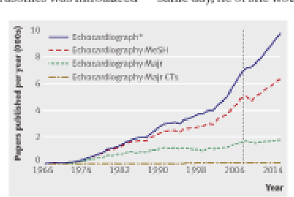

Fig 1 | Trends in numbers of papers listed each year in PubMed, according to search strategies 1-4 in table. The numbers to the right of the vertical line, after 2009, are projected totals. MeSH=medical subject heading, Majr=as a main topic; CTs=controlled clinical trials

Results

The table shows the publications retrieved by each search, along with totals for the last full calendar year. Figures 1 and 2 show annual totals to 2009 and predictions from 2010 until 2015.

Search 5 without the cardiovascular system gave 700 011 citations. A search for "diagnostic imaging" [Mesh] and "cardiovascular system" [Mesh] gave 195 106 papers, or 159 661 if limited to human studies, core clinical journals, and Medline.

To estimate the time that it might take a new entrant to the subspecialty to read all the previous literature, we assumed that he or she could read five papers an hour (one every 10 minutes, followed by a break of 10 minutes) for eight hours a day, five days a week, and 50 weeks a year; this gives a capacity of 10 000 papers in one year. Reading all papers referring to echocardiography (search 1) would take 11 years and 124 days, by which time at least 82 142 more papers would have been added, accounting for another eight years and 78 days. Before our recruit could catch up and start to read new manuscripts published the same day, he or she would—if still alive and even remotely interested—have read 408 049 papers and devoted (or served a sentence of) 40 years and 295 days. On the positive side, our recruit would finish just in time to retire.

Reading only the major studies would need more than four years for strategy 3 and more than five years for strategy 6. Alternatively, if only one year was allocated for study, then for strategy 3 our recruit would need to read 95 papers every single day. If our recruit kept to the European Working Time Directive, he or she would have to read 138 papers a day, or for strategy 6, 162 papers a day at a rate of one every three minutes.

To keep up to date, the cardiac imaging specialist needs to read 30 papers a week on echocardiography or 43 a week on multimodality imaging. If limited to one paper every working day (estimated total 250 a year), then the chance that he or she will read any particular paper is 1 in 8.9. The chance that a colleague on the opposite side of the world will read that same paper in the same year is 1 in 79. If each reads a random selection of 250 papers a year, then the median number that both will read can be estimated at 28 (range 16-40) or 1.3% of the total.

A search strategy restricted to evidence on outcomes would not work for this subspecialty. The

Search strategies for identifying articles on diagnostic imaging in cardiology

Strategy	Question	Total no of papers from 1966 to September 2010	Papers published in 2009
1	All papers that include any reference to echocardiography	113 976	7207
2	All papers cited with echocardiography as medical subject heading	84 689	4672
3	All papers with echocardiography as a main topic	34 577	1558
4	Papers with echocardiography as a main topic, restricted to human controlled trials	457	23
5	All papers referring to the cardiovascular system and any one of multiple imaging modalities cited as a medical subject heading; referred to in text as any "multimodality imaging"	109 604	7083
6	All papers referring to the cardiovascular system or diagnosis of cardiovascular disease and any one of multiple imaging modalities, if cited as a main topic and limited to humans; referred to in text as major "multimodality imaging"	40 496	2226

On the impossibility of being expert

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Not just the *difficulty*, mind, but the

impossibility

search:

‘diagnostic imaging’ AND ‘cardiovascular system’:

195 106

limited to:

human studies, core clinical journals, Medline:

159 661

Assume you read:

5 papers/hour

8 hours/day

5 days/week

50 weeks/year

10 000 papers/year.

Being an expert in echocardiography

Reading all existing papers: **11 years and 124 days**.

Meanwhile 82142 more papers added: another **eight years and 78 days.**

Before catching up, you need to read 408049 papers devoting **40 years and 295 days** to it.

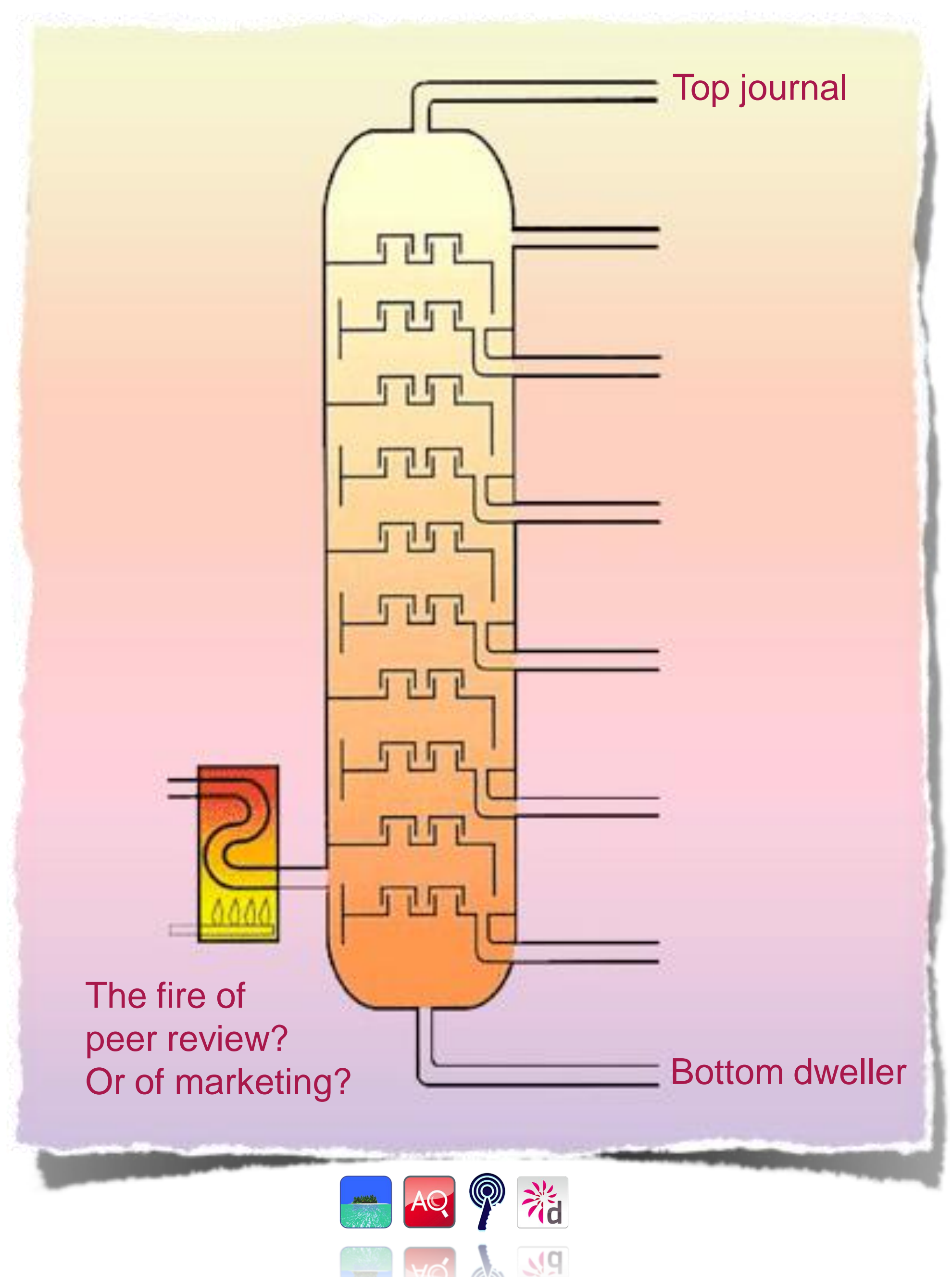
You would finish just in time to retire.

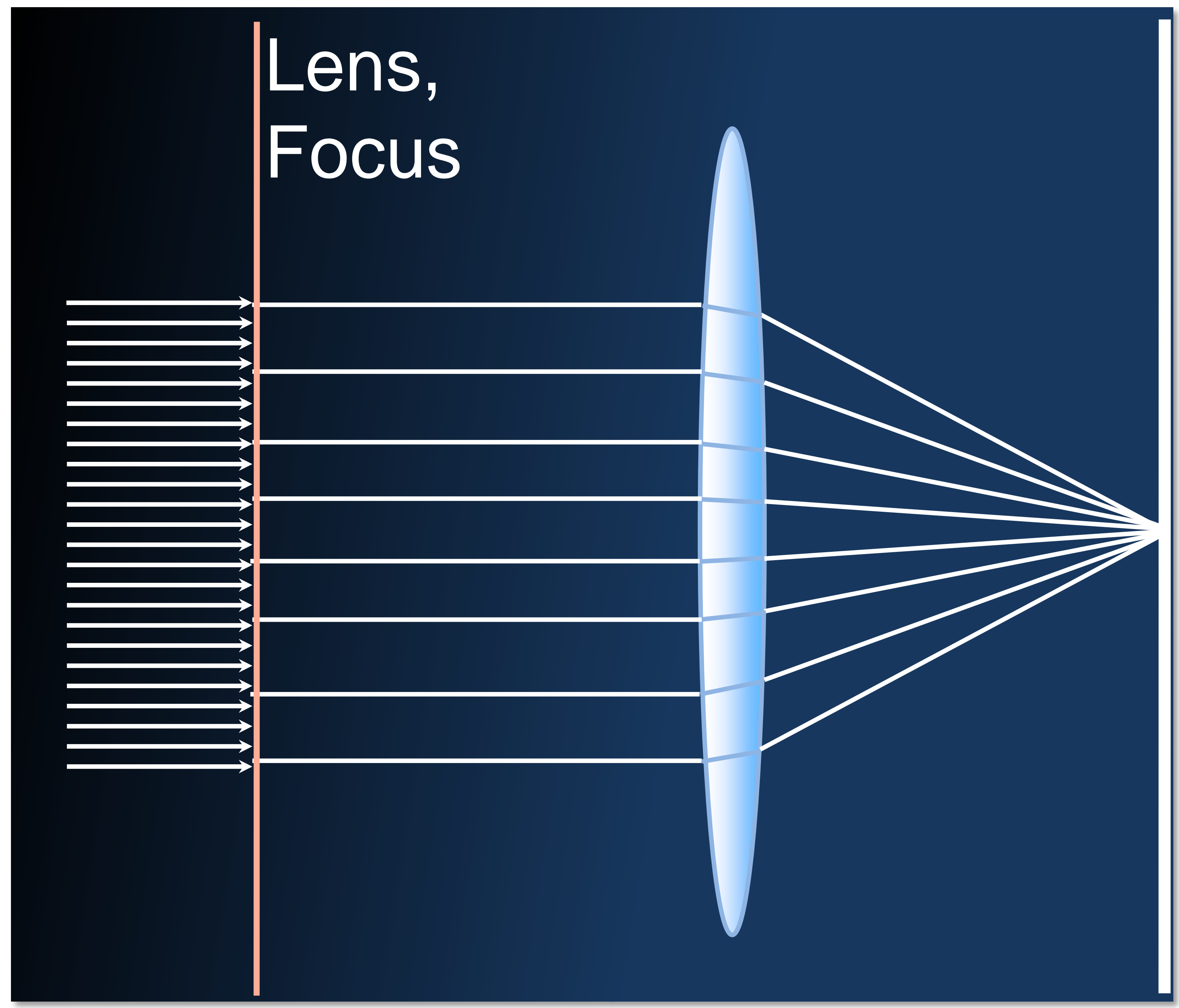
Speed of new relevant articles appearing

Speed of being able to read articles

Read it all? — Signal to noise low!

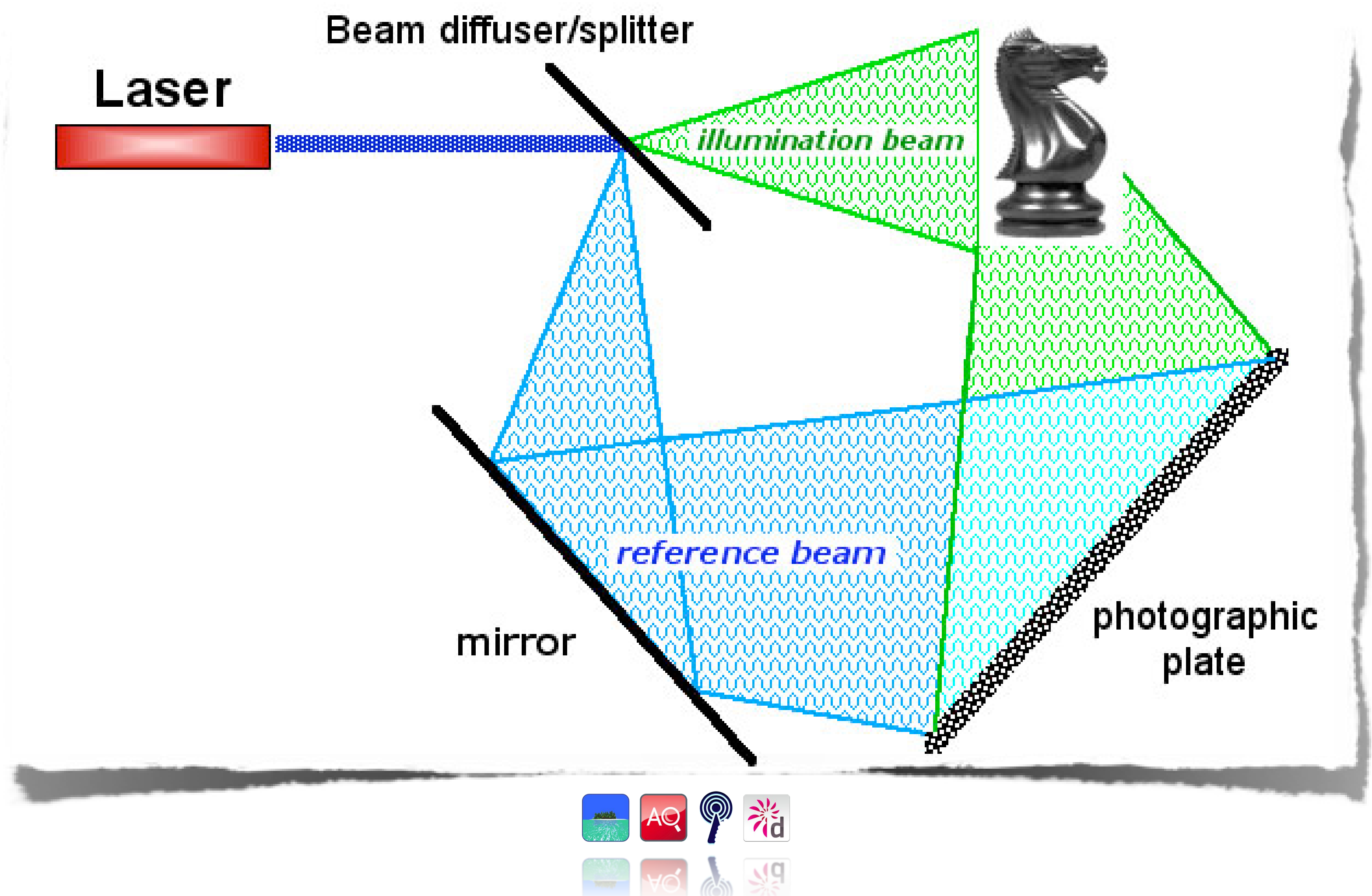
Filter, Distill?




Lens,
Focus

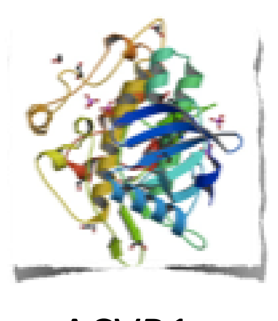
Or maybe something more sophisticated?

hologram?



Semantic triples

Semantic triples



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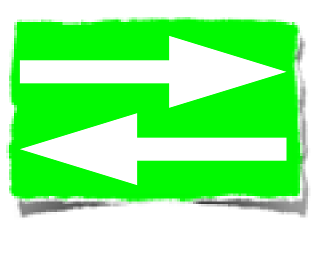

is associated with

Fibrodisplasia

Concept ‘Triples’ are language independent

Jan Velterop	presented	these slides
Johannes Velterop	vertoonde	deze dia’s
JJM Velterop	zeigte	diese Transparantien
J Velterop	présentait	cettes diapositives
燕 德维尔村	显示	这些幻灯片

- The entities have URIs.
- This allows for disambiguation of synonyms & homonyms, so that the conceptual content of an assertion can be reflected, irrespective of the actual words used.

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ACVR1 | Search

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(5Z)-7- ACVR1 Ethyl alcohol Malaria Metabolomics Naphthalene Pyro Ru-Tuss Liquid Safety Biomarkers, Drug Shoe Spirit Spiritualities aspirin bace2 biomarkers, drug safety bis(hydroxy-2-ethylthio)-1,10-decane d2d ethanol fibrodysplasia ossificans progressiva malaria naphthalene p53 pde5a shoes silent spirit

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Search Search

Concept 3a6c5bd1-29b0-4946-b1a4-74e909a0cdf4

ACVR1 (Homo sapiens)

by ConceptWiki (all)

ACVR1 (Homo sapiens) ACVRLK2

ACVR1 (Homo sapiens)

by SwissProt

Gene or Genome

ACVR1 (Homo sapiens) ACVRLK2

Notations
UniProt Q04771

Urls
http://www.uniprot.org/uniprot/Q04771

associated labels

ACVR1 (Homo sapiens) ACVRLK2

2 most recent searches

acvr1, ACVR1

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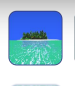

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Concept 41c76d76-d676-4e95-9dc0-12b10ebe9257

associated_with

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associated_with

associated_with

by UMLS

has a significant or salient relationship to.

associated_with

Notations
Unified Medical Language System T166

associated labels
associated_with

3 most recent searches
associated_with, acvr1, ACVR1

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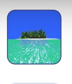
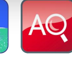

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Concept ceeee1f7-203b-445b-9860-e9acffd46fa6

Fibrodysplasia Ossificans Progressiva

by ConceptWiki (all)

Fibrodysplasia Ossificans Progressiva

Fibrodysplasia Ossificans Progressiva

by UMLS

Disease or Syndrome

Fibrodysplasia Ossificans Progressiva

Notations

Unified Medical Language System	C0016037
Medical Subject Headings	D009221

Urls

http://purl.bioontology.org/ontology/NCIM/C0016037
http://purl.bioontology.org/ontology/MSH/D009221

associated labels

Fibrodysplasia Ossificans Progressiva

4 most recent searches

fibrodysplasia ossificans progressiva, associated_with, acvr1, ACVR1

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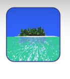
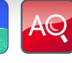

ACVR1

is associated with

Fibrodysplasia Ossificans Progressiva

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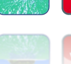

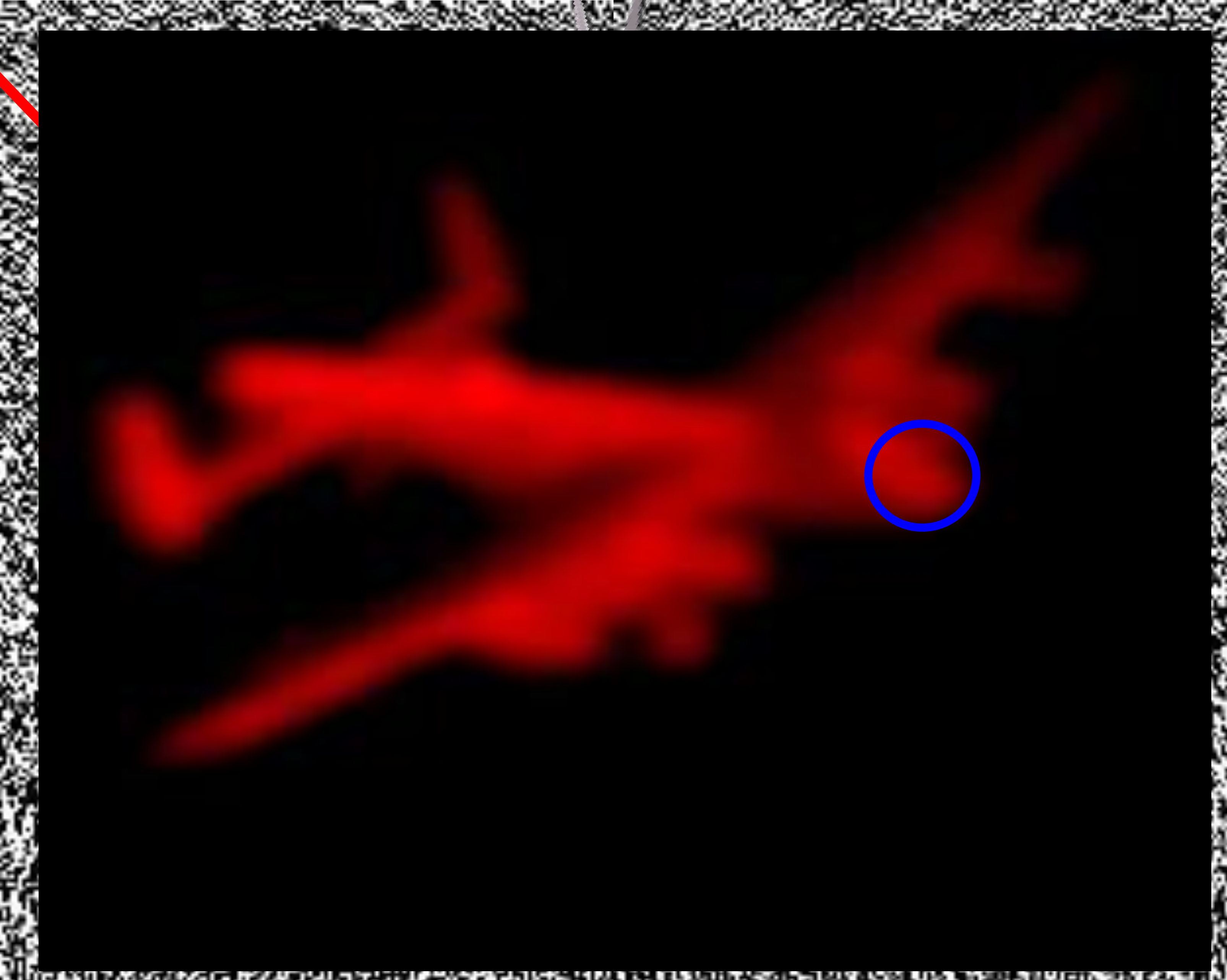

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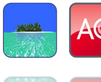

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is associated with

Fibrodysplasia Ossificans Progressiva

This ‘assertion ‘ – triple – can also be enhanced with meta-information, such as provenance

And then it becomes a ‘nanopublication’

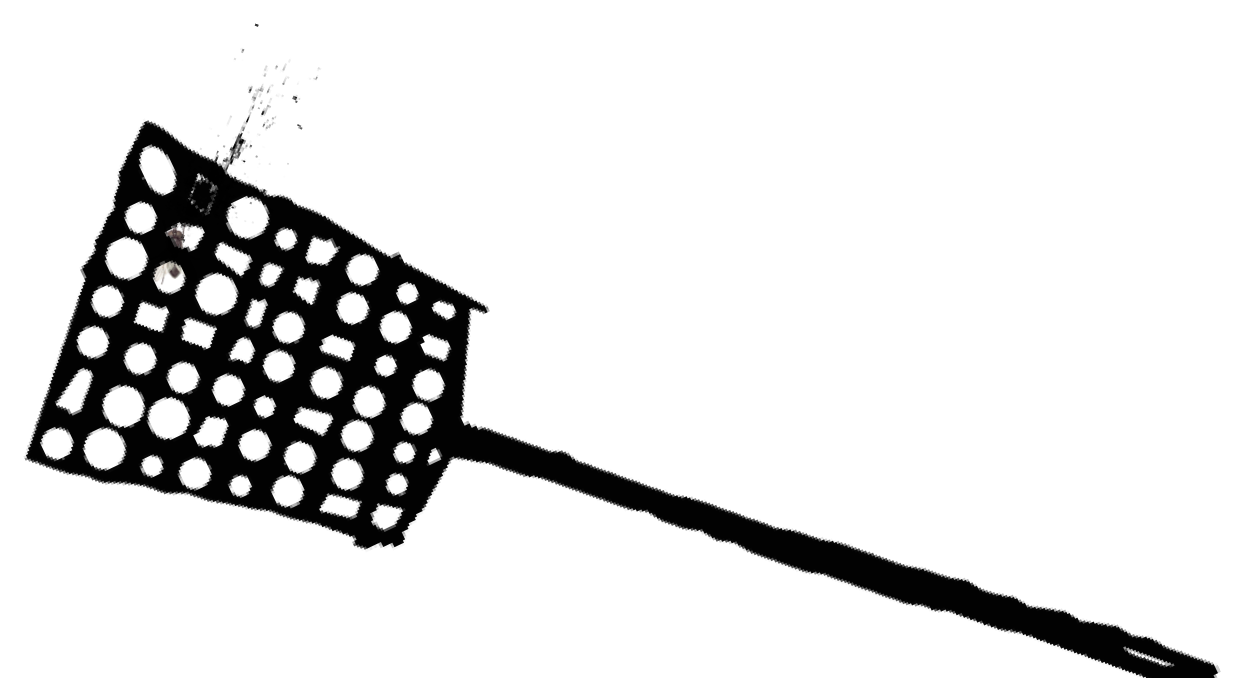
Nanopublication?

Triple with attribution, provenance

Definition

- A nanopublication is a single, machine-readable, citable scientific assertion along with associated provenance.
- *Nano* refers just to its *smallness*
- *Publication* refers to its cite-ability; a nanopublication is the smallest possible textual publication that may be scientifically meaningful

- Publishers can extract and expose the nanopublications contained in their publications
- They conceptually ‘link’ data and literature, and foster citation of the literature



Challenge:
to convert literature to nano-publications

On-the-fly

Why nanopublications and not just triples?

Nanopublications come with the idea that their authors/providers may gain credit for the use of these assertions by others

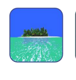
Because we don't just live in a **knowledge** economy, but also in an **acknowledge** economy (the 'ego-system')

- Nanopublications can be cited and thus may credit authors, journals, databases, publishers
- And they are ‘linked’ – at least ‘linkable’ (URIs) – combatting the fragmentation of information that’s the bane of science

http://nanopub.org

Caveat

- Nanopublications, even very large collections of nanopublications, do not – cannot – reflect full scientific reality in all its nuances
- But they help give direction, overview, hypothesis creation, etc.



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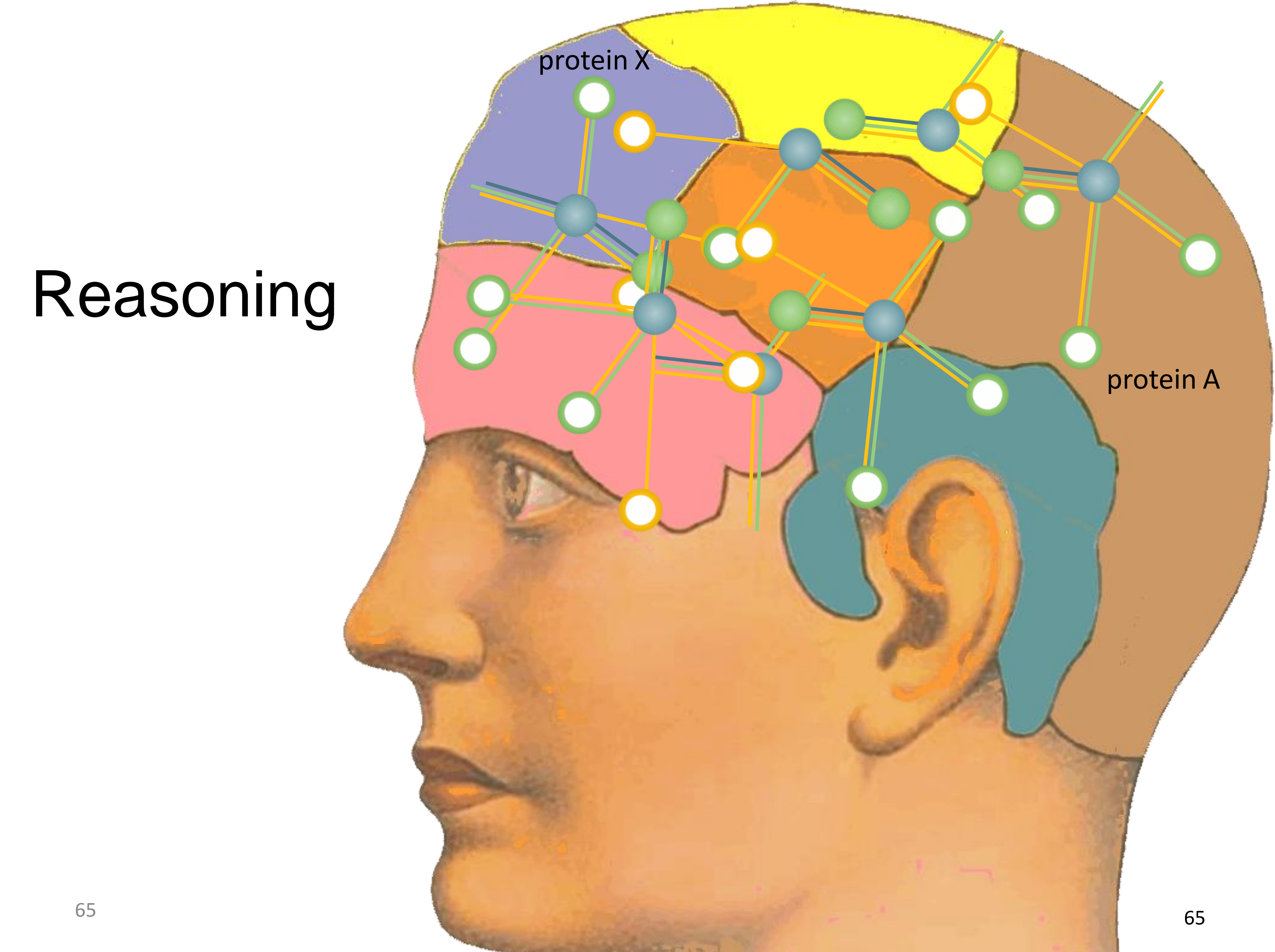
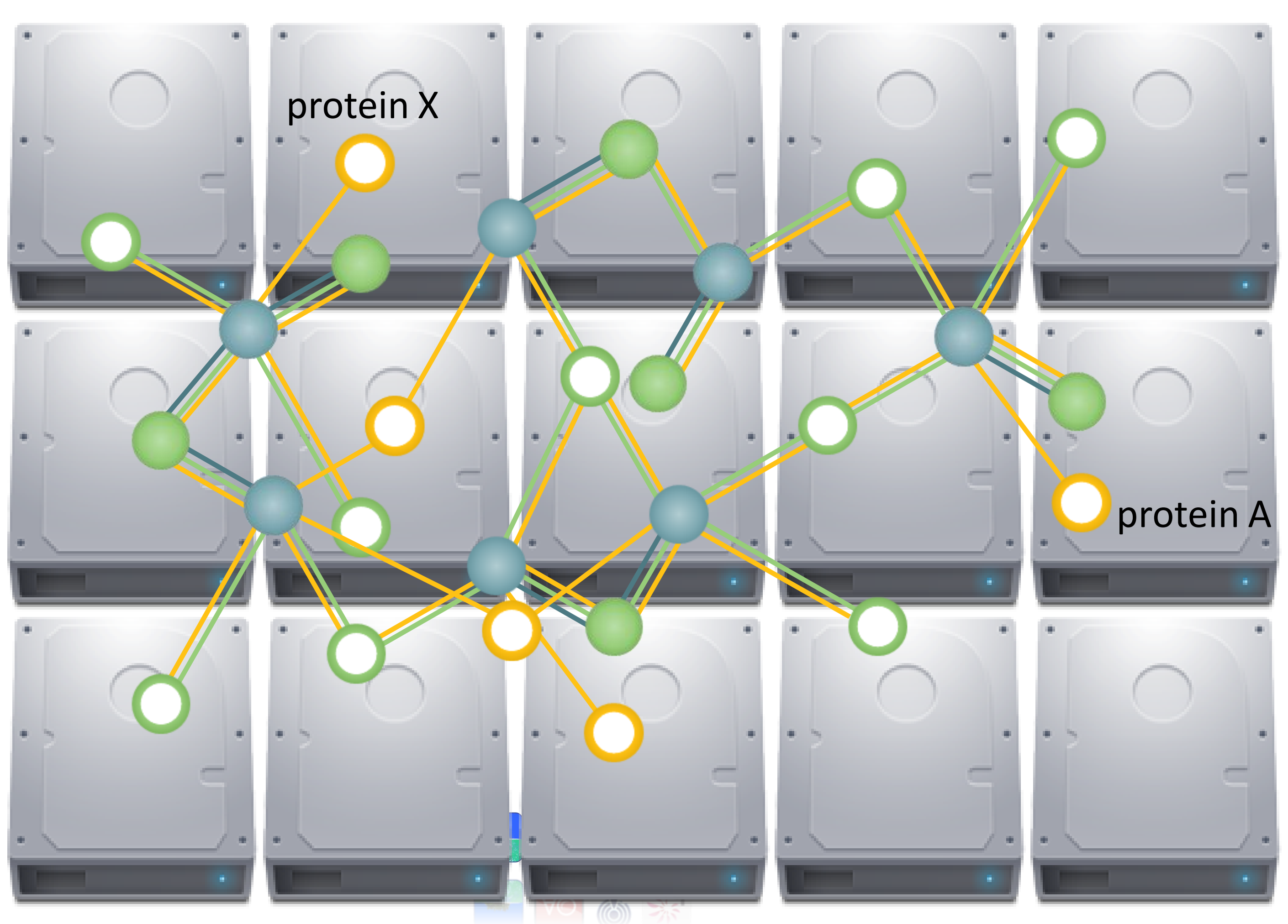


65

Triples (including nanopublications) can also be used to reason – ‘*in silico*’ – and therefore on a much larger scale



The upshot:

"Faced with information overload, we have no alternative but pattern recognition.”

Marshall McLuhan

Example

The ‘nanopublication’ approach is being taken by the Innovative Medicine Initiative project Open PHACTS, aimed at significantly speeding up drug discovery

http://www.openphacts.org/open-phacts-explorer

Open PHACTS

Open PHACTS

Open PHACTS Explorer

Navigation

- Compound
  - Compound by name
  - Compound by structure
- Target
  - Target by name
- Pharmacology
  - Pharmacology by Enzyme family
  - Pharmacology by Compound
  - Pharmacology by Target

Help and Feedback

API Status

TSV Downloads

Pharmacology by Compound name

Hint: Type in compound name. E.g. "Aspirin" and select a result

Compound name: Sildenafil Search...

Filter Provenance: On Off

Pharmacology by Compound name search results - Total Records: 250

Prepare tsv file

	Structure	Compound Name	Target Names	Target Organisms	Assay Organism	Assay Description	Activity Type	Relation	Value	Units	SMILES
1		Sildenafil	HERG	Homo sapiens	Homo sapiens	Inhibition of human Potassium channel HERG expressed in mammalian cells	IC50	=	5480	nM	O=S(=O)(N1CC.
2		Sildenafil	Phosphodiesterase 5A	Homo sapiens	Homo sapiens	Inhibition of phosphodiesterase type 5 (PDE5) of human platelets	IC50	=	1.6	nM	O=S(=O)(N1CC.
3		Sildenafil	Phosphodiesterase 1A Phosphodiesterase 5A Phosphodiesterase 1B	Bos taurus Homo sapiens Bos taurus		Relative inhibition of bovine heart PDE1 and PDE5 of human platelets	IC50 ratio	=	140		O=S(=O)(N1CC.
4		Sildenafil	Phosphodiesterase 2A Phosphodiesterase 5A	Rattus norvegicus Homo sapiens		Relative inhibition of PDE2 of rat kidney and PDE5 of human platelets	IC50 ratio	>	10		O=S(=O)(N1CC.

The semantic approach is also being taken by this Open PHACTS exemplar:

Free semantic scientific PDF viewer
http://utopiadocs.com

Utopia Documents – Just One Position–Independent Lysine Residue Can Direct MelanA into Proteasomal Degradation following N–Terminal Fusion of Ubiquitin

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Just One Position-Independent Lysine Residue Can Direct MelanA into Proteasomal Degradation following N-Terminal Fusion of Ubiquitin

Christian Setz[1], Melanie Friedrich[1], Sabine Hahn[1], Jan Dörrie[2], Niels Schaft[2], Gerold Schuler[2], Ulrich Schubert[1]*

1 Institute of Clinical and Molecular Virology, Universitätsklinikum Erlangen, Erlangen, Germany, **2** Department of Dermatology, Universitätsklinikum Erlangen, Erlangen, Germany

Abstract

N-terminal stable in frame fusion of ubiquitin (Ub) has been shown to target the fusion protein for proteasomal degradation. This pathway, called the Ub fusion degradation (UFD), might also elevate MHC class I (MHC-I) antigen presentation of specific antigens. The UFD, mainly studied on cytosolic proteins, has been described to be mediated by polyubiquitination of specific lysine residues within the fused Ub moiety. Using the well characterized melanoma-specific antigen MelanA as a model protein, we analyzed the requirements of the UFD for ubiquitination and proteasomal degradation of a transmembrane protein. Here we show that fusion of the non-cleavable Ub^{G76V} variant to the N-terminus of MelanA results in rapid proteasomal degradation via the endoplasmic reticulum-associated degradation (ERAD) pathway and, consequently, leads to an increased MHC-I antigen presentation. While lysine residues within Ub are dispensable for these effects, the presence of one single lysine residue, irrespectively of its location along the fusion protein, is sufficient to induce degradation of MelanA. These results show that the ubiquitination, ER to cytosol relocation and proteasomal degradation of a transmembrane protein can be increased by N-terminal fusion of Ub at the presence of at least one, position independent lysine residue. These findings are in contrast to the conventional wisdom concerning the UFD and indicate a new concept to target a protein into the ubiquitin-proteasome system (UPS) and thus for enhanced MHC-I antigen presentation, and might open up new possibilities in the development of tumor vaccines.

Citation: Setz C, Friedrich M, Hahn S, Dörrie J, Schaft N, et al. (2013) Just One Position-Independent Lysine Residue Can Direct MelanA into Proteasomal Degradation following N-Terminal Fusion of Ubiquitin. PLoS ONE 8(2): e55567. doi:10.1371/journal.pone.0055567

Editor: Sadashiva Karnik, Cleveland Clinic Lerner Research Institute, United States of America

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Competing Interests: The authors have declared that no competing interests exist.

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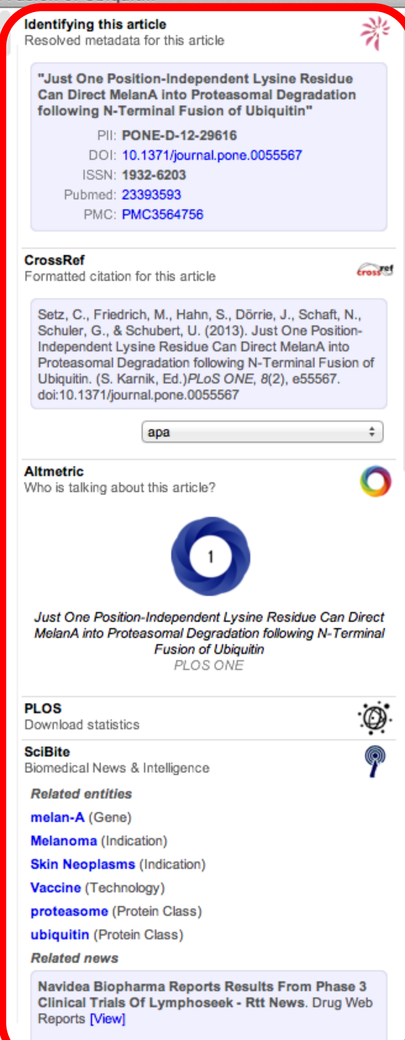

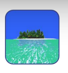

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Jus[…]dependent Lysine Residue Can Direct MelanA into Proteasomal Degradation following N-Terminal Fusion of Ubiquitin

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1 Institute of Clinical and Molecular Virology, Universitätsklinikum Erlangen, Erlangen, Germany, **2** Department of Dermatology, Universitätsklinikum Erlangen, Erlangen, Germany

Abstract

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Received September 27, 2012; **Accepted** December 27, 2012; **Published** February 5, 2013

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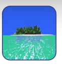
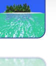
Funding: This work was supported by a grant IE-S08T06 from the German Human Genome Research Project, by the grant SFB 643-A1 from the German Research Council as well as by National Institutes of Health grant R01DK81553. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Competing Interests: The authors have declared that no competing interests exist.

* E-mail: ulrich.schubert@viro.med.uni-erlangen.de





The semantic approach is being taken by this Pharma intelligence service, too:

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Toricelli M et al Mol Cancer. 2013 Mar 25;12(1):22. (4 days ago)

TIMP metallopeptidase inhibito.. | melan-A | integrin, beta 1 (fibronectin .. | CD63 molecule | Melanoma | Skin Neoplasms | integrin beta | fibronectin | metallopeptidase inhibitor | Gene-Gene Link | Gene-Disease Link | Biomarker

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melan-A

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Setz C et al PLoS One. 2013;8(2):e55567. doi: 10.1371/journal.pone.005... (49 days ago)

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Ramos-Vara JA et al Vet Pathol. 2013 Jan 31. (55 days ago)

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Journal of Molecular Biology

Volume 386, Issue 1, 13 February 2009, Pages 190–203

Structural Insights into the Association between BCAR3 and Cas Family Members, an Atypical Complex Implicated in Anti-Oestrogen Resistance

Marie-Line Garron[1, 2, 3, †, 2], Diana Arsenieva[1, 2, 3, †, 3], Jessie Zhong[4, 5], Alexander B. Bloom[6], Adam Lerner[6], Geraldine M. O'Neill[4, 5], Stefan T. Arold[1, 2, 3,]

[1] INSERM, U554, 34090 Montpellier, France

[2] CNRS, UMR5048, Centre de Biochimie Structurale, 2, 34090 Montpellier, France

[3] Universités Montpellier 1 and 2, 34090 Montpellier, France

[4] Focal Adhesion Biology Group, The Oncology Research Unit, The Children's Hospital at Westmead, New South Wales 2145, Australia

[5] Discipline of Paediatrics and Child Health, University of Sydney, Westmead, New South Wales 2006, Australia

[6] Department of Medicine, Section of Hematology and Oncology, Boston University Medical School, Boston, MA 02118, USA

http://dx.doi.org/10.1016/j.jmb.2008.12.010, How to Cite or Link Using DOI

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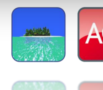

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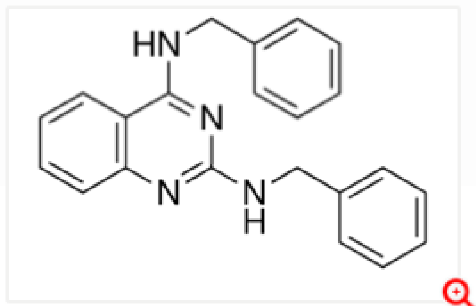
Synonym: JRF 12, N2,N4-dibenzylquinazoline-2,4-diamine

Empirical Formula (Hill Notation) $C_{22}H_{20}N_4$ | Molecular Weight 340.42 | MDL number MFCD03691820



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Properties

Related Categories	Apoptosis Inducers, Apoptosis and Cell Cycle, Autophagy, Autophagy Inhibitors, Bioactive Small Molecules, More...
assay	≥98% (HPLC)
form	powder
color	yellow
solubility	DMSO: ≥20 mg/mL
storage temp.	room temp

Price and Availability

SKU-Pack Size	Availability	Price (GBP)	Quantity
SML0031-5MG	BACKORDERED - Estimated delivery date 19.04.2013	57.50	0
SML0031-25MG	BACKORDERED - Estimated delivery date 19.04.2013	230.00	0

Bulk orders?

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Description

Frequently Asked Questions

Live Chat and Frequently Asked Questions are available for this Product.

Biochem/physiol Actions

DBeQ is a potent and specific inhibitor of ATPase p97, an integral component of the ubiquitin-fusion degradation (UFD) pathway. DBeQ inhibits the degradation of ubiquitinated proteins, the endoplasmic reticulum-associated degradation pathway, and autophagosome maturation. The compound also potently inhibits cellular proliferation and induces caspase 3/7 activity and apoptosis.

	Molecules, More...
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Scientific publications *remain important*

For the record (Minutes of Science)

But perhaps not for reading

And perhaps not in journals

But to provide the raw material for knowledge pattern recognition

Thank you!

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