CLINICAL INNOVATION: Fair & Effective Incentives for New Uses of Established Drugs

Second Medical Uses: Missed opportunities, clinical successes & what the data tells us

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Panellists:

- **Prof. Graham Russell** *NDORMS, University of Oxford*
- **Dr David Cavalla** *Numedicus*
- **Dr Amitava Banerjee** *UCL Farr Institute of Health Informatics*

Second Medical Use: Missed opportunities, clinical successes & what the data tells us about missed opportunities

Prof. Mondher Toumi
SMU Conference, Washington
February 9,2018

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Agenda

1. Patent the cornerstone
2. Off label use of generics and biosimilars
3. Governmental off label use recommendation
4. HTA the major resistance
5. Pricing a discouraging step

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Patent The corner Stone of Second Medical Use Medicine (1/2)

- Second medical use of medicine before substance patent expiry is subject to an agreement with the IP owner or restricted to the IP owner
- When a product falls off patent then developing a new indication become possible under the condition you are not challenged by the use off label of the generics or biosimilars
- To avoid or limit off patent use of generics or biosimilars a patent become critical in many circumstances

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Patent The corner Stone of Second Medical Use Medicine (2/2)

- The return on investment of developping a new medicine is primarely driven by the sales in US.
- In Europe there are large uncertainties on the ability to get access and a relevant price
- So it is important to achieve access in the US
- Data protection nd market exclusivity in EU is 10 years, and 3 to 5 years in US, and zero in most developping countries
- Without a patent for second use, data protection in US is too short to permit to recup the investment and in EU there are too much uncertainty

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Second Medical Use Patent

- It has become extremely difficult to obtain a second medical use patent in US
  - Especially if the examiner originate from a specific country

The level of expectation and the resistance to scientific, common sense argument render such patenting almost unachievable making multiple company to drop the development of highly critical therapies in area of major unmet needs for patients suffering extremely severe conditions

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Clopixol

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Scizophrenia

- Schizophrenia is a severe condition associated with delusion, hallucination, dissociation and cognitive disturbance
- Mortality related to schizophrenia is higher than HIV patients 10 years ago
- 20% of patients are resistant to all available therapies and are treated with clozapine

- Clozapine is asociated to major agranulocytosis leading to death.
- It's use is very limited and most patients do not receive it because of side effects

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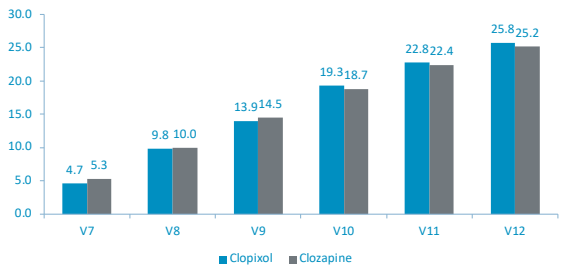
Clopixol

	Clopixol	Clozapine
	N=120	N=117
% Reduction, mean(SD)	0.24 (0.10)	0.23 (0.12)
Response rate	62 (51.67%)	56 (47.86%)

ANCOVA adjusted tests : *P<0.05; **P<0.005; ***P<0.0005

PANSS total score varies from 30 to 210



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Clopixol

Clopixol is an approved antipsychotic, proven to be as effective as clozapine in treatment-resistant schizophrenia (TRS) based on a large double blind randomized trial may support a patent use?
Clopixol was not available in US.

Patent for second use in that indication was refused because a skill in the art would have tried clopixol in that population as it is an antipsychotic

However in more than 30 years and million of patients treated there have not been a single public report of use of clopixol in that population

After 6 years of battles and expert report the opinion of the examinor was unchanged

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VLB-01

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Background

- VLB has been historicaly developed in Russia within academic institution
- Development was halted following disruption of Soviet Union.
- It was patented only in Russia for the treatment of epilepsia and was then shelved
- The product was later acquired by a western company and was under re-development by Marco Polo Pharmaceuticals (MPP).

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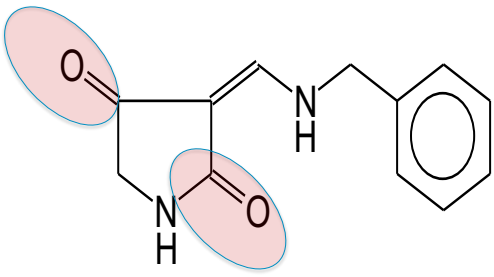
VLB-01 Receptor Profiling



- A large screening has shown that VLB-01 is acting exclusively on the ML2 *(MT3/QR2)* receptor

There are no exemple of aproved product or in development product with such mode of action

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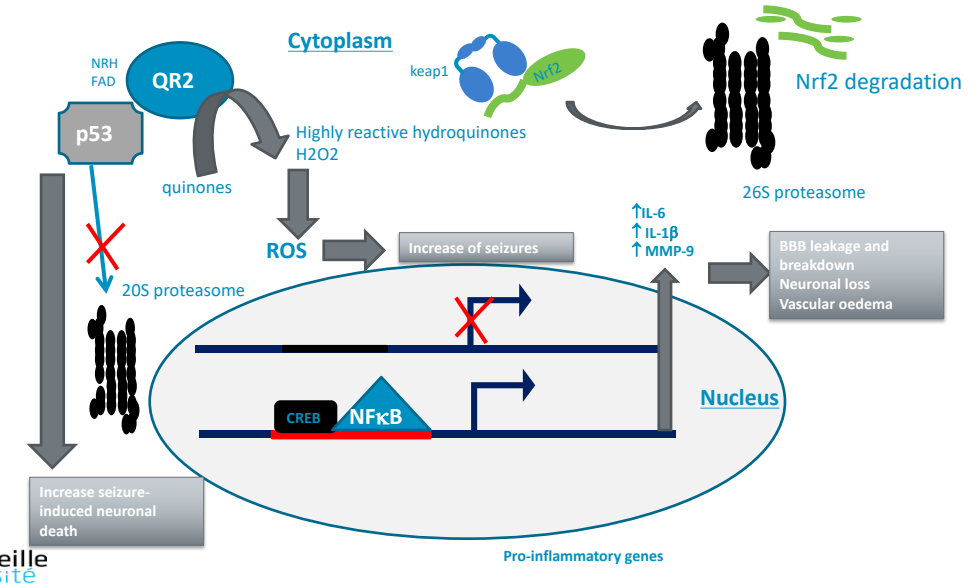
Summary of QR2-related mechanisms in epilepsy



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VLB-01
Preclinical Data in other CNS Models

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Patent?

- VLB-01 has the potential to be a pain killer, an antipsychotic and a bipolar disorder therapy
- Examiner: as VLB-01 is an antiepileptic, it has as many antiepileptic the potential to treat all those conditions
- There are no products known or approved targeting MT3 receptor. All the work on the receptology and mode of action was not considered by the examinor

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Unique Opportunity Lost For Severe Conditions

- This is a second example of a unique therapy abandonned despite a very promising opportunity for millions of patients being poorly serviced
- The patentability limitation in US has become a real hurdle to access to innovative effective and safe second use therapy for patients
- The lack of revenue of start up make difficult to raise money to challenge the patent office

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Off Label Use of Generic or Biosimilar

- Once a product got a patent for a second got a patent for a second medical use indication one need to secure the product will not be facing competition from generics or biosimilar because the same substance is being used
- Changing dosage, mode of administration, formulation may help but not always
- Often the risk of biosimilar or generic competition discourage the development

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Example of RANKL Inhibitors

- With a patent use of RANKL inhibitors for their efficacy in the regulation of male fertility (preclinical and clinical evidence)
- NewCo may use the approved therapy Denosumad, a monoclonal antibody RANKL inhibitor
- Because of short term use and high value by avoiding Medically Assisted Procreation, the price will be significantly higher than current Desonumab
- Denosumab patent expiration is planned in 2021 implying the launch and plausible competition from off label use of biosimilars
- This is a possible catch 22 situation unless a smart way to overcome the off label use of the biosimilar

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Lucentis Avastin

Avastin is an EVGF developped for oncology by Roche. Avastin has shown to be effective in Age-Related Macular Degeneration

Roche and Novartis agreed to develop Lucentis (similar to Avastin) for DMLA but much more expensive

In UK Avastin is used in ophtalmology clinics instead of Avastin

In France the government allowed off label use of avastin instead of Lucentis

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Temporary Recommendation for Use (RTU): Avastin® for Financial Reason

Article L. 5121-12-1 of public health code issued from law of December 29,2011 authorized the French Agency for the Safety of Health Products (ANSM) to elaborate a Temporary Recommendation for Use (RTU) to a drug that already has a marketing authorization (MA) in France, to be used for another indication(s) not conform to its MA.

Avastin Marketing authorization indication

Avastin is a cancer medicine used in combination with other medicines to treat :

- Adult patients with metastatic carcinoma of the colon or rectum
- Metastatic breast cancer
- Unresectable advanced, metastatic or recurrent non-small cell lung cancer
- Advanced and/or metastatic renal cell cancer
- Epithelial ovarian, fallopian tube or primary peritoneal cancer

RTU indication for Avastin: The treatment of age-related macular degeneration

RTU established in 24/06/2015 and started in 01/09/2015

RTU is valid for 3 years renewable

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HTA the Most Critical Hurdle in EU

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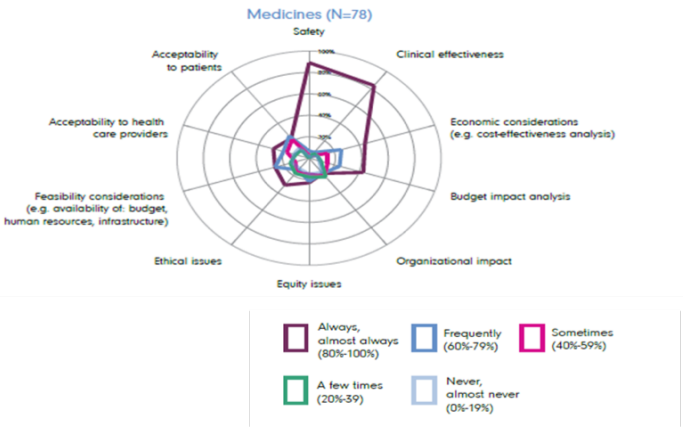
Current HTA Decision Frameworks and Challenges

Attributes & Deliberative Process

Frequency of covering different aspects in HTA (among 10 pre-specified aspects of HTA)

WHO "2015 Global Survey on Health Technology Assessment by National Authorities"



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Current HTA Decision Frameworks and Challenges f

HTA Eligibility

- Second use medicines may not be eligible to HTA in some countries, e.g. categorised as generic medicines, even though they may have significant additional benefit versus already approved formulations of the same active substance

- Second use medicines may not be eligible to early HTA scientific advice, i.e., not considered "enough innovative", while these products may highly benefit from HTA bodies feedback on their clinical development plan

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Siklos an Interesting Story

- Sickle cell syndrom is a severe hematologic rare condition targeting young children and treated with an oncology product off label Hydrea. The product is an IV formulation while it is used oraly by children
- 29th of June 2007 Addmedica is granted a MAA for a new formulation developped for sikle cell syndrom for children named Siklos
- The HTA considered Hydrea as the comparator and concluded at a minor benefit with no comparative evidence
- The pricing committee set the price of Siklos® at €67 (1000 mg) and €13.40, whereas the average EU price was €550 and €110 for the 1000 mg and 100 mg pack, respectively.
- A long court case with multiple procedures in front of various juridictions supported the pricing committee decision. Ultimately the product was not made available in France

Conclusion

- Current regulation happen to prevent multiple second use medications to reach the market despite a very high potential public health impact
- Multiple opportunities exist: orphan designation, new indication extension, pediatric extension, PUMA program etc.
- If no options are feasible then public funding should support development of such opportunities
- Action is warranted to avoid such society massive loss of opportunities

New Uses for Existing Drugs

UCL & Georgetown University Law Center

7-9th February 2018

Graham Russell MD PhD FRS

Professor of Musculoskeletal Pharmacology.

The Botnar Research Centre,

University of Oxford, UK

BRC

and

Sir Edward Mellanby

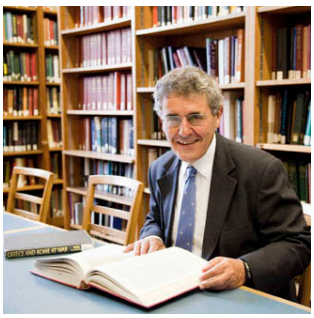
The Mellanby Centre for Bone Research

University of Sheffield, UK

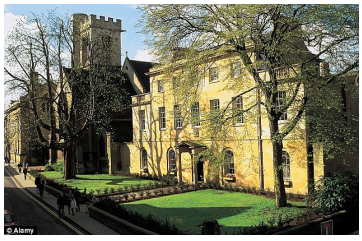
The University Of Sheffield.

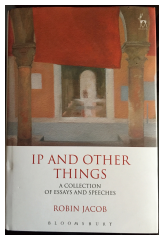
Thank you for the invitation!

St Peter's College, Oxford



Sir Robin Jacob

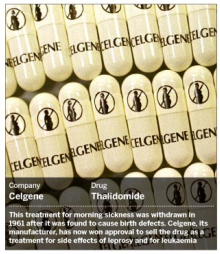




New Uses for Existing Drugs
The role of Serendipity!

Thalidomide

From morning sickness and medical disaster to treating leprosy and myeloma

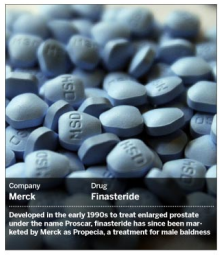


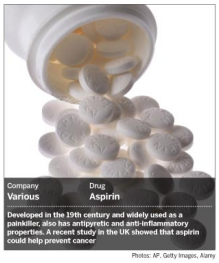
Sildenafil (Viagra)

From anti-hypertensive to treating erectile dysfunction and pulmonary hypertension

Finasteride

From treating prostate enlargement to male baldness





Photos: AP, Getty Images, Alamy

Aspirin

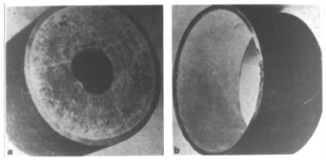
From pain killer to preventing cardiovascular disease and cancer

Musculoskeletal Diseases

- Very common
- Fractures
- Osteoporosis (>30% over 50)
- Sports injuries
- Consequences of trauma
- Osteoarthritis
- Rheumatoid Arthritis (1% of population)
- Other types of arthritis (>100)
- Pagets diseases (3% > 50 yrs)
- Cancer metastases (breast, prostate), and myeloma

- Less common
- >450 rare inherited diseases eg Brittle bones, dense bones etc

Bisphosphonates. A 48+ year Journey From Water Softeners to Blockbuster Drugs

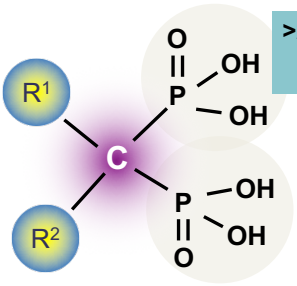


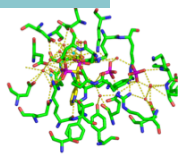
Towards a molecular explanation of actions of bisphosphonates

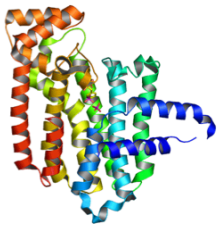
Davos

Russell RG. Bisphosphonates: The first 40 years. Bone. 2011 Jul;49(1):2-19

>27,000 publications in PubMed

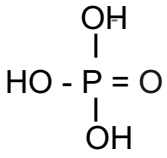




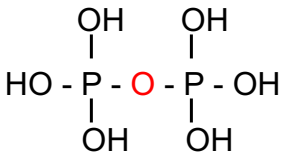


Risedronate in Farnesyl Pyrophosphate Synthase

Chemical Relationships. Phosphates, Pyrophosphate and Bisphosphonates



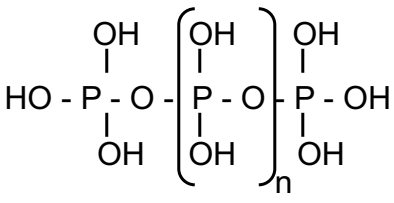
Inorganic Phosphate (Pi)



Inorganic Pyrophosphate (PPi)

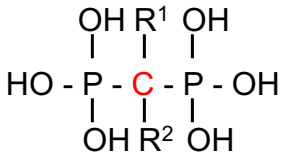
Chemically and Enzymatically Labile

Nature's "water softener"



Inorganic Polyphosphate as acid, where n = 1 to 100+

(eg Graham salt)



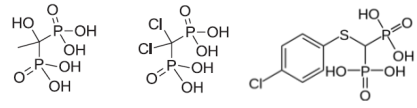
Bisphosphonate (BP) as acid

Chemically Stable

Used as medicines

Clinically Utilised Bisphosphonates. Different Mechanisms of Action

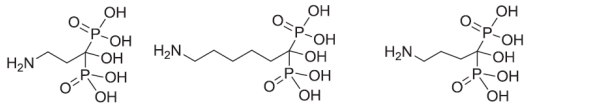
- **Early BPs: non-nitrogen containing**



Etidronate Clodronate Tiludronate

Incorporated into ATP analogues

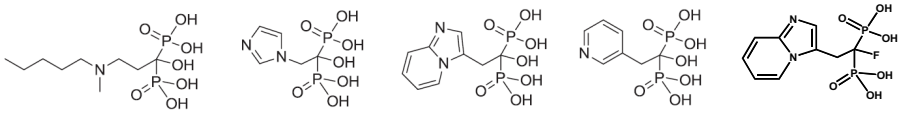
- **"Second" generation: nitrogen-containing with short alkyl chains**



Pamidronate Neridronate Alendronate (Fosamax)

N-BPs inhibit FPPS enzyme in mevalonate pathway

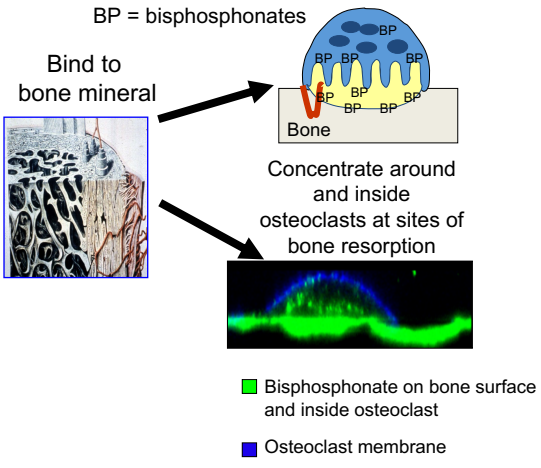
- **"Third" generation: (from medicinal chemistry optimisation): nitrogen-containing with branched or ring structure**



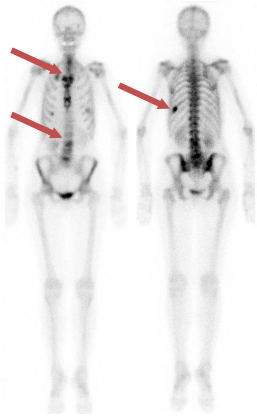
Ibandronate Zoledronate Minodronate Risedronate

Ox-14, a new BP

Bisphosphonates Are Taken Up Avidly By Bone



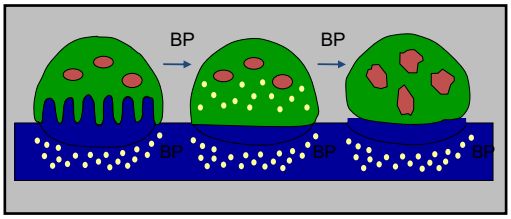
Technetium-99m-labelled BP locates selectively to cancer sites in bone



The bisphosphonates have tissue selectivity for bone

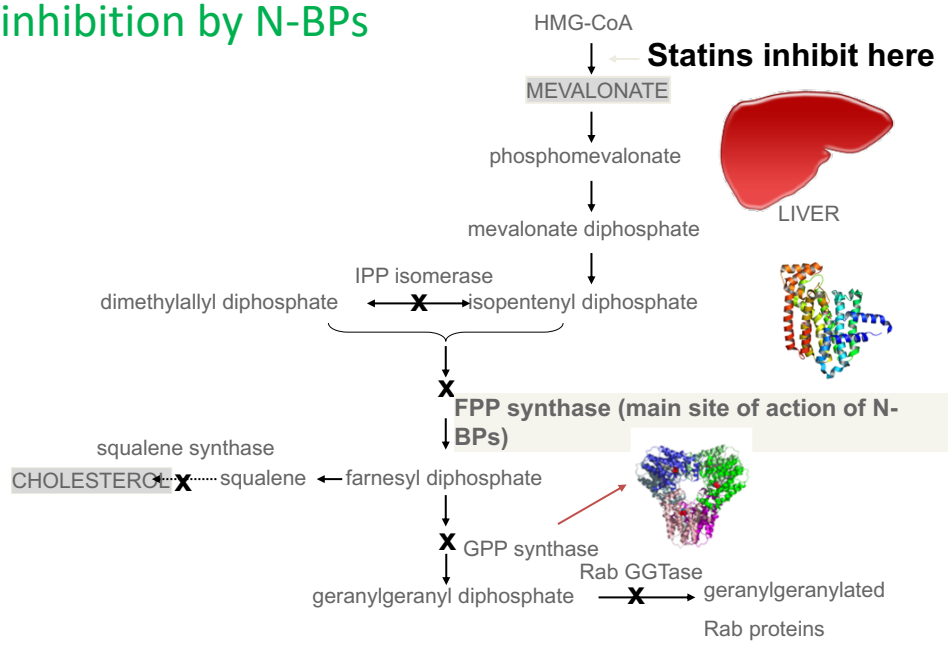
Bisphosphonates Act by Inhibiting the Mevalonate Pathway in Osteoclasts

Michael Rogers



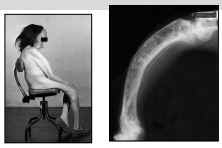
From Rogers, Reska, Russell 2002

Mevalonate pathway. Multiple sites of inhibition by N-BPs

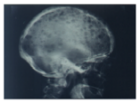


Bisphosphonates are Used to Treat Many Bone Resorption Disorders

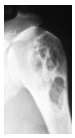
Paget's Disease



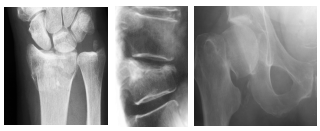
Myeloma



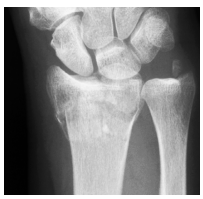
Bone metastases



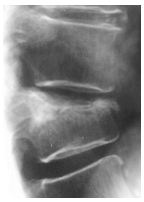
Osteoporosis



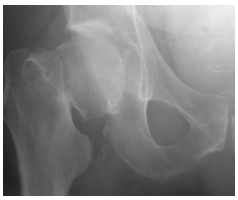
Bisphosphonates are Used to Prevent Fractures In Osteoporosis



Wrist

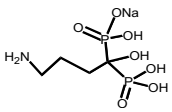


Spine

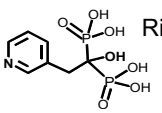


Hip

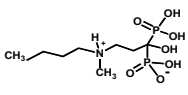
Oral "blockbuster" BPs



Alendronate

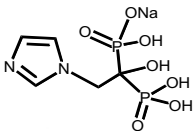


Risedronate

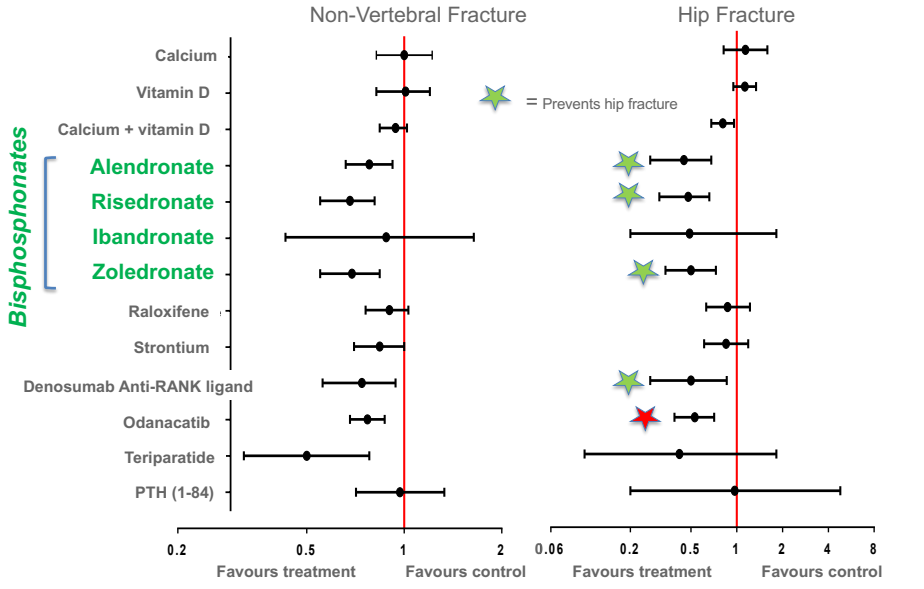


Ibandronate

Zoledronate is given once yearly iv

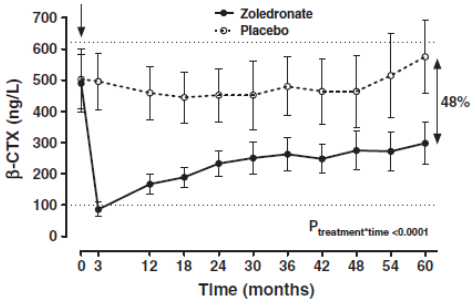


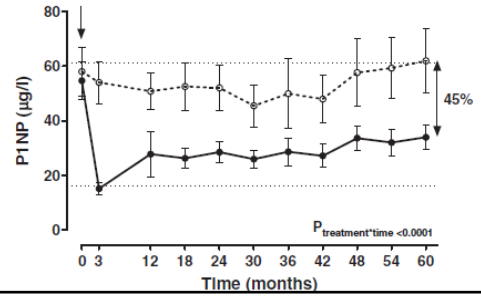
Drugs Used to Prevent Fractures



Adapted from Reid 2016

Zoledronate has a remarkably long duration of action!





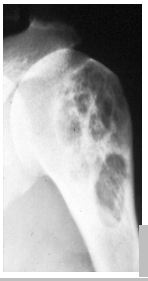
CTX is a biomarker of bone resorption

Osteopenic Women Given just 1 Infusion of Zoledronate 5mg

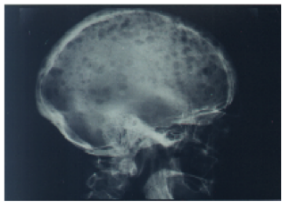
PINP is a biomarker of bone formation

Grey et al, . Bone 50:1389, 2012

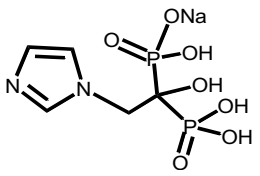
Bisphosphonates (esp Zoledronate) Are Used to Prevent Skeletal Related Events (SREs) In Cancer
(Hypercalcaemia, Bone Loss And Fractures etc)



Humerus with lytic lesions in breast cancer



Skull with lytic lesions in myeloma



Zoledronate (iv)

Note that alendronate and risedronate were never developed for treating cancer, despite being oral drugs

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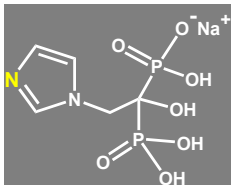
The Zoledronate Story



Zoledronate (iv)

A Novartis Invention

Given Iv only, not oral

Standard of care for bone metastases and myeloma

Very effective in osteoporosis

Remarkably long duration of action (>1 year after only one dose of 5mg); basis for patent, contested, and patent revoked

Extensively studied for biological effects

>3700 refs in PubMed

Several potential medical uses not developed because of patent expiry

eg Bone erosions in rheumatoid arthritis,

New applications, DNA repair etc

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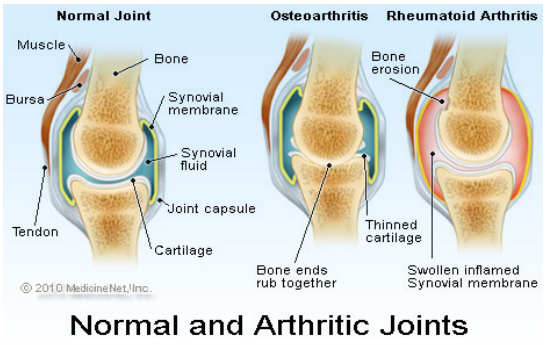
Bone Erosions In Rheumatoid Arthritis Lead To Deformity And Disability



Normal and Arthritic Joints

Bisphosphonates have never been properly assessed in Rheumatoid Arthritis

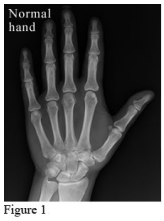


Figure 1

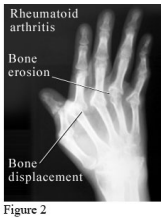
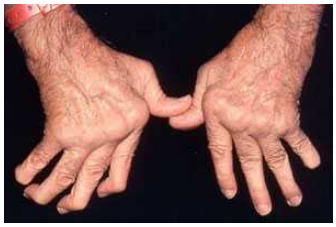


Figure 2



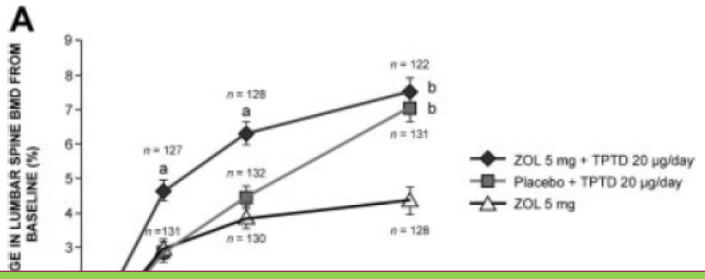
Old Dogs and New Tricks

Examples of potential additional medical uses of Bisphosphonates

- Rheumatoid erosions, inflammatory bone loss
- Osteoarthritis,
- New formulations (eg oral zoledronate)
- Combinations with other drugs
  - In osteoporosis
  - Combination with chemotherapeutic agents in cancer

Combining Zoledronate with Teriparatide (TPD; parathyroid hormone) Produces a Larger Increase in Bone Mass in Osteoporosis

Post-menopausal woman with OP (mean age 65, LS T-score -2.8)



But unlikely to ever be developed as an approved indication because of size and high cost of clinical trials to demonstrate greater reduction of fractures

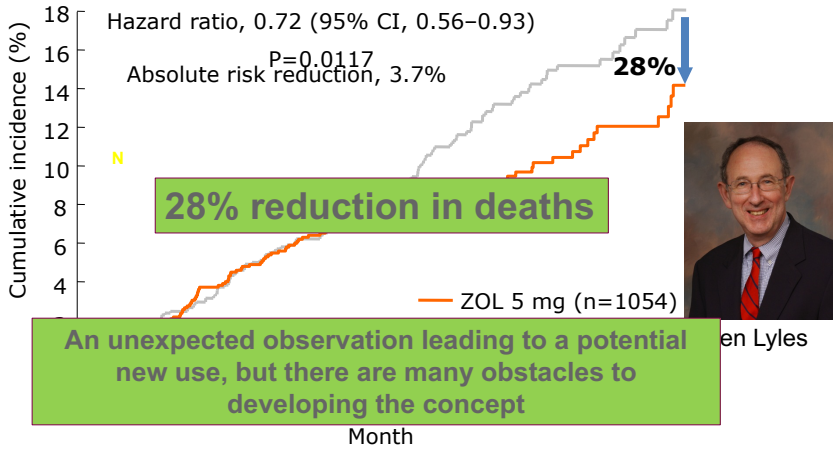
Cosman et al, JBMR 2011

Examples of Potential Non-Skeletal Effects of Bisphosphonates

(derived from clinical observations)

- Reducing colon cancers
- Reducing heart attacks and heart failure
- Increasing survival in intensive care units
- Preventing radiation damage by enhancing DNA repair and tissue regeneration.
- Reducing mortality and extending life span ("senolytics")

Zoledronate Reduced Risk of All-cause Mortality by 28% Over Time in Hip Fracture Trial



en Lyles

An unexpected observation leading to a potential new use, but there are many obstacles to developing the concept

Lyles KW, et al. *N Engl J Med*. 2007;357:1799–809.

Bisphosphonates Reduce the Risk of Myocardial Infarction in Patients with Rheumatoid Arthritis

ORIGINAL ARTICLE

JBMR

Bisphosphonate Use Is Associated With Reduced Risk of Myocardial Infarction in Patients With Rheumatoid Arthritis

Frederick Wolfe,[1] Marcy B Bolster,[2] Christopher M O'Connor,[3] Kaleb Michaud,[4] Kenneth W Lyles,[3,5,6] and Cathleen S Colón-Emeric[3,5]

28% reduction in heart attacks

- National Databank for Rheumatic Diseases, prospective study of RA patients, 2002-2011
- n=19,281. Number of patients ever on bisphosphonate: 5,891
- HR for MI among treated patients 0.72 (0.54-0.96) when on BP therapy compared to when on no therapy

Wolfe, F.et al Journal of Bone and Mineral Research, Vol. 28, No. 5, May 2013, pp 984–991-1

Reduction of in-hospital mortality in patients who were treated with bisphosphonate prior to ICU admission

J Clin Endocrinol Metab. 2016 May;101(5):1945-53

Preadmission bisphosphonate and mortality in critically ill patients

Paul Lee[1,5,7,8], Carmen Ng[2], Anthony Slattery[4], Priya Nair[3,7], John A. Eisman[1,6,7,8], Jacqueline R. Center[1,6,7]

Department of Endocrinology[1], Pharmacy Department[2], Intensive Care Unit[3], PET and Nuclear Medicine[4], St Vincent's Hospital; Diabetes and Metabolism Division[5], Bone Biology Division[6], Garvan Institute of Medical Research, Faculty of Medicine[7], University of New S Wales, School of Medicine University of Notre Dame, Sydney, NSW, Australia

- 7830 critically ill patients admitted to Intensive Care Unit (ICU) between 2003 and 2014.
- 245 patients received preadmission bisphosphonate.
- Bisphosphonate users were older (66±16 vs. 58±18 years, p<0.01) and had greater co-morbid disease burden (Charlson co-morbidity index: 5.7±3.6 vs. 4.6±3.8, p<0.01), yet bisphosphonate use was associated with a lower in-hospital mortality [Mortality Rate Ratio (MRR): 0.41 (95% CI 0.24–0.71, p<0.01)]

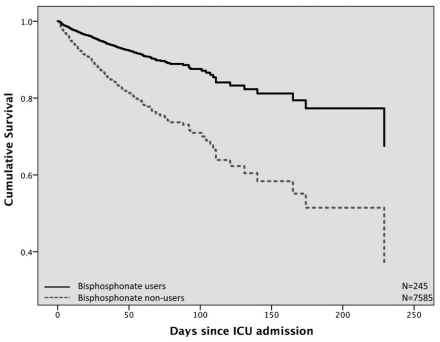


Figure 2. Bisphosphonate and survival Survival curves comparing bisphosphonate users and nonusers.

59% reduction of in-hospital mortality in patients who were treated with bisphosphonate pre-ICU admission

STEM CELLS

TISSUE-SPECIFIC STEM CELLS

Zoledronate Attenuates Accumulation of DNA Damage in Mesenchymal Stem Cells and Protects Their Function

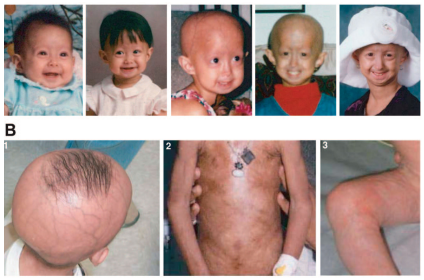
JUHI MISRA,[a] SINDHU T. MOHANTY,[a] SANJEEV MADAN,[b] JAMES A. FERNANDES,[b] F. HAL EBETINO,[c,d] R. GRAHAM G. RUSSELL,[a,e] ILARIA BELLANTUONO[a]

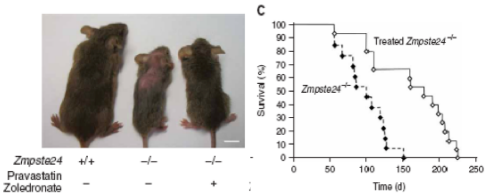
[a]Mellanby Centre for Bone Research and MRC-Arthritis Research Centre for Integrated Research into Musculoskeletal Ageing (CIMA), Department of Human Metabolism, Medical School, University of Sheffield, Sheffield, United Kingdom; [b]Department of

Key Words. Stem cells • DNA damage • Aging • Radiation • mTOR • Bisphosphonates

Zoledronate can protect human mesenchymal stem cells from radiation damage and cellular ageing

Accelerated Ageing
Hutchinson-Gilford Progeria Syndrome (HGPS).





HGPS is due to a genetic defect in prenylation

Life span in mouse model is doubled by giving zoledronate plus a statin

Clinical trials in progress

"New Tricks", "Repurposing"
New Uses for Existing Drugs

Telegram from the Queen on 100th birthday!

Can we all live to 100?!

Metformin
From Type 2 diabetes to anti-ageing and Altzheimers

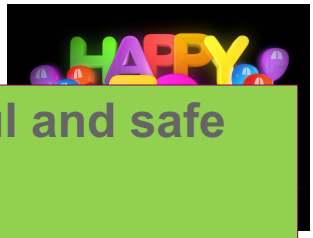
Rapamycin
From immunosuppressant to anti-ageing

Resveratol
Red wine

Bisphosphonates
From bone diseases to anti-ageing and DNA repair

Can We Change the Road Signs?!

Bisphosphonates approach 50th Birthday! Party in 2019



50 years of successful and safe clinical use.

Many new uses for unmet medical needs are possible if current legal, commercial, and logistic barriers are reduced.

Thank You!

Examples of Open Access Research Without Patents

- The Human Genome Project
- The Structural Genomics Consortium (SGC; Oxford, Toronto & Karolinska)

- **The Structural Genomics Consortium (SGC)**

- A public-private partnership that supports the discovery of new medicines through open access research.
- To avoid the duplicative and unsuccessful aspects of industrial research
- Many successes of SGC include depositing more than 1500 high-resolution structures of medically relevant human and parasite proteins into the public databases
- Production of freely available reagents and drug probes
- See http://www.sgc.ox.ac.uk

Chas Bountra

Chief Scientist SGC Oxford

David Cavalla

Numedicus

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Misconceptions

- DRP does not identify ground-breaking drugs
  - Alemtuzumab (formerly CamPATH for CLL; now MS)
  - Pirfenidone (formerly anthelmintic for IPF)
  - Ketamine (from anaesthesia to severe depression)
  - Espindolol (hypertension to cachexia)
- Big pharma is not interested
  - Access to failed assets and data from pharma companies (MRC, NCATS)

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No money in repurposing?

- Tecfidera (dimethyl fumarate); Namenda (memantine)
  - Peak sales $2.91bn; $0.8bn
- Modafinil, thalidomide, gabapentin
  - Repurposed for various orphan (& non-orphan) diseases
  - All billion-dollar products
  - Companies developed sales franchises
  - Thalidomide became lenalidomide (PYS $4.28bn); modafinil became armodafinil; gabapentin became pregabalin
  - Indications expanded with new CoM-protected analogue
- Raloxifene
  - Original discovery objective to identify alternative SERM to treat tamoxifen-resistant breast cancer
  - Repurposed to osteoporosis
  - Retrospective evidence showed it prevented breast cancer recurrence
  - Peak sales $1.09bn

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Acetyl salicylic acid, 2000 years after Herodotus

- Aspirin first marketed by Bayer in 1899, for pain
- In 1970s, John Vane shows it disrupts platelet aggregation; effective for MI & stroke
- In 2010, shown to prevent GI and other cancers (25,000 pts) [Rothwell, 2010]
- Hazard ratio for pancreatic cancer = 0.25

Retrospective evidence in cancer

Cancer type	Drug type
Breast	Beta-blockers
Colorectal	Calcium-channel blockers
Liver	HMG CoA inhibitor
Lung	Na^+/K^+ ATPase inhibitor
Melanoma	Metformin
Oesophageal	NSAIDs
Ovarian	PPAR agonists
Pancreatic	Quinolone antibiotic
Prostate	TNF antagonists
Stomach	

…but sometimes not repeated prospectively (metformin in pancreatic cancer)

Other indications…

Age related macular degeneration	Depression	Pneumonia
Alzheimer disease	Diabetes (type II)	Psoriasis
Asthma	Epilepsy	Rheumatoid arthritis
Autism	Glaucoma	Sepsis
Burn injury	Influenza	Stroke
Cachexia	Myocardial infarction	Systemic vasculitis
Cataracts	Osteoporosis	Transplant rejection
Chronic renal failure	Parkinson disease	
COPD	Periodontitis	

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