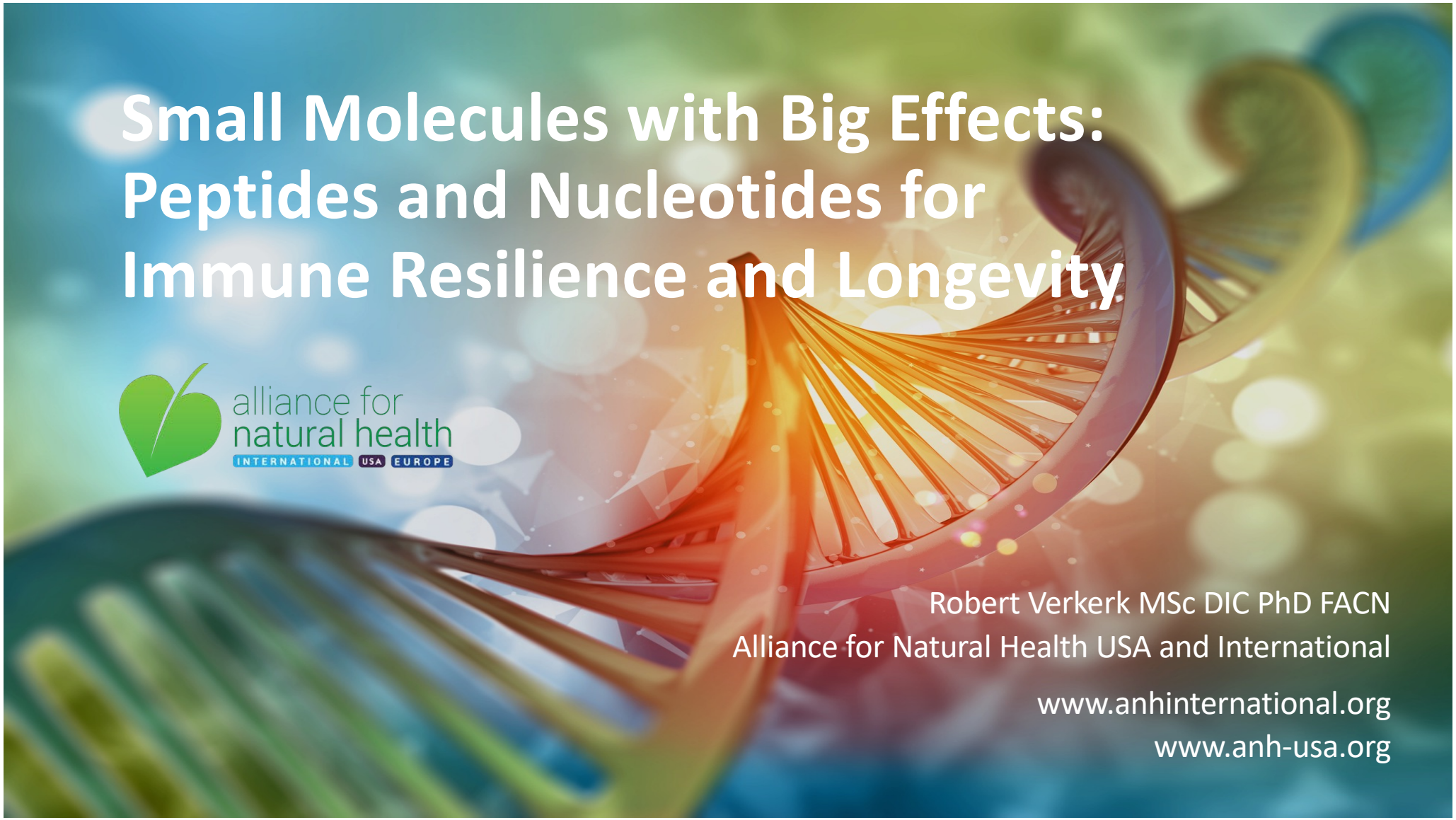
Small Molecules with Big Effects: Peptides and Nucleotides for Immune Resilience and Longevity



alliance for natural health
INTERNATIONAL USA EUROPE

Robert Verkerk MSc DIC PhD FACN
Alliance for Natural Health USA and International

www.anhinternational.org
www.anh-usa.org

Declaration of interests – my journey with nucleotides and peptides

- Consultancy with ProBio (Switzerland) since 2009 – global leader in research and manufacture of nucleotides for animal and human health
- Consultancy with Nucleotide Nutrition Ltd — UK-based supplier of nucleotides for human health
- Consultant to Profound Health/Nutrition – manufacturer and distributor of Khavinson bioregulatory peptides

HOW SMALL?

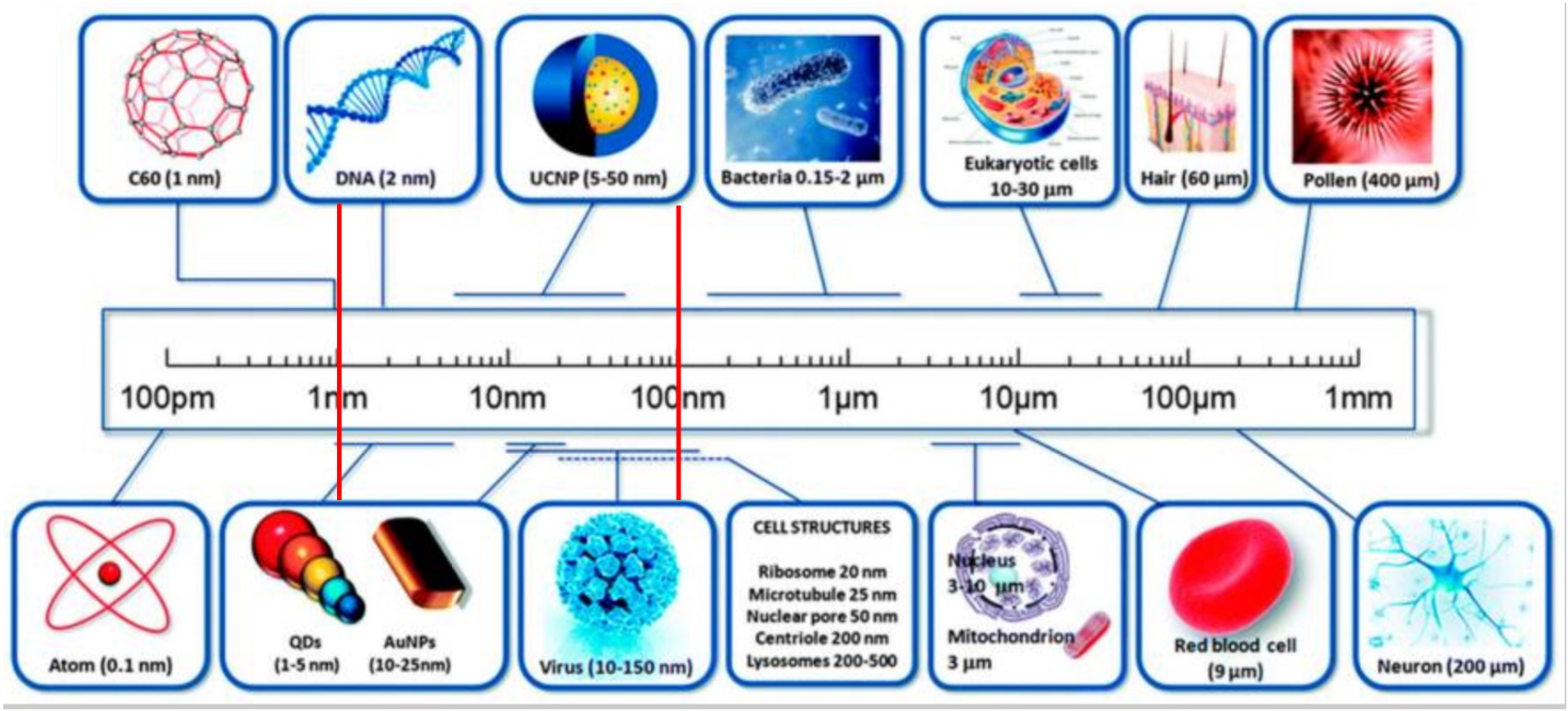
Definitions

- **Nanomaterials**—Any organic, inorganic, or mixed (organometallic) material that presents distinct chemical, physical, and/or electrical properties owing to their ultrasmall size, typically in the nanoscale region (most often from 1 nm up to a few to several tens of nanometers).
- **Natural nanomaterials**—A nanomaterial made by nature through bio- or geo-chemical or mechanical processes, without direct or indirect connection to a human activity or anthropogenic process.
- **Incidental nanomaterials**—A nanomaterial unintentionally produced as a result of any form of direct or indirect human influence or anthropogenic process.
- **Engineered nanomaterials**—A nanomaterial conceived, designed, and intentionally produced by humans.
- **Anthropogenic nanomaterials**—Both incidental and engineered nanomaterials.

Note: The definition of "nanomaterial" is still an active area of scientific and policy debate, although small size, high surface area, and enhanced reactivity over bulk materials are universally accepted requirements. The definition given above is currently well within the mainstream of current thought and acceptance.

Hochella MF, et al. *Science* 2019; 363: eaau8299.

Size comparisons



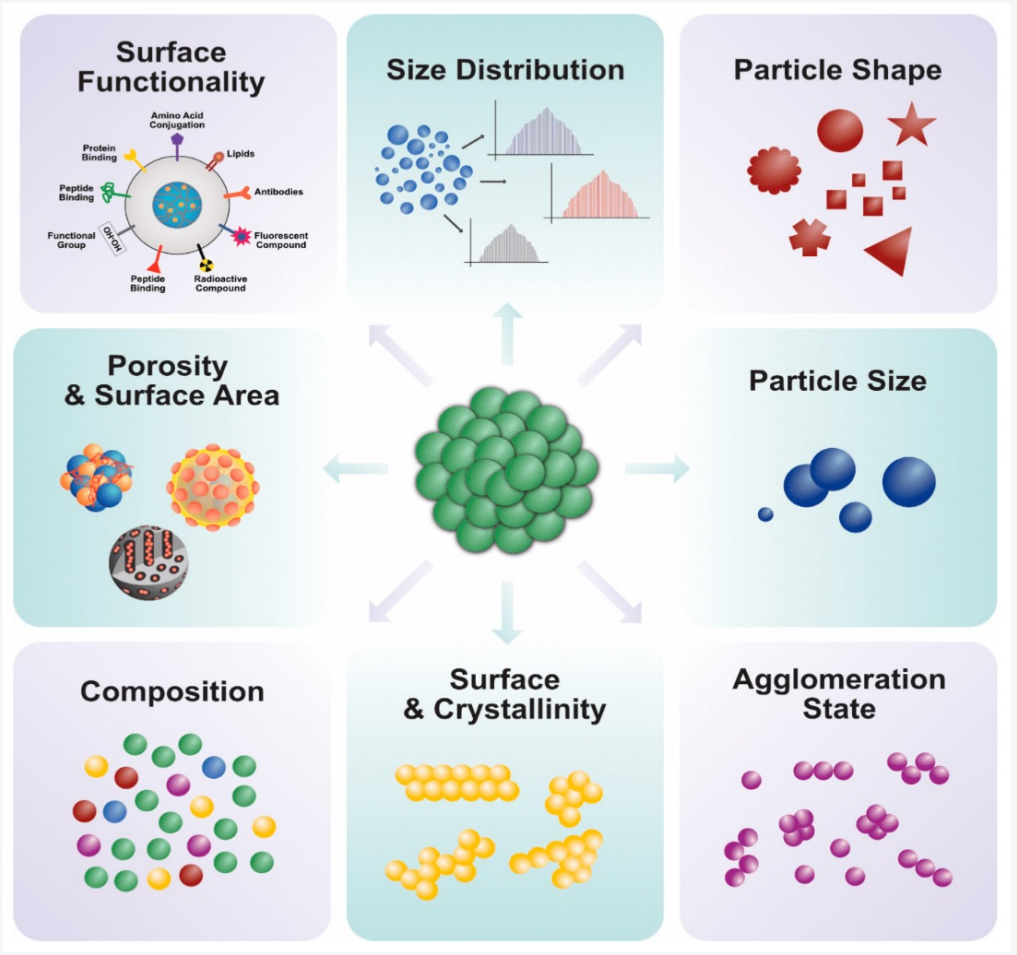
Bayda S et al. *Molecules* 2020; 25(1): 112.

Examples of natural nanos and nanotechnology as applied to human health

Nano biomolecules	Nanotechnology*
Vitamins	Targeted delivery of drugs and genes
Minerals	Vaccines (with/without injection)
Nucleosides and nucleotides	Cosmetics and cosmeceuticals
Amino acids	Imaging
Peptides	Diagnostics
Botanicals (secondary plant compounds)	Regenerative medicine: bone and neural tissue
Liposomes	Novel gene sequencing (nanopore-based)

*Sources: National Nanotechnology Initiative
Hu X, et al. *Front Bioeng Biotechnol.* 2020; 8: 990.

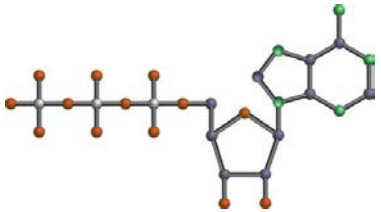
Properties of nanomaterials



Jeyaraj M, et al. *Nanomaterials.* 2019; 9(12):1719.

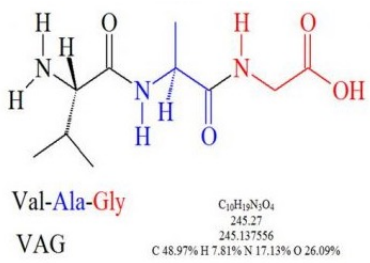
NUCLEOTIDES and PEPTIDES – THEIR RELATIONSHIP TO DNA & RNA

Fundamentally speaking….



Nucleotides – components

- Building blocks of RNA & DNA
- Endogenous + exogenous sources



Regulatory peptides – interaction

- Interact directly with DNA
- Protein synthesis, gene expression, signalling

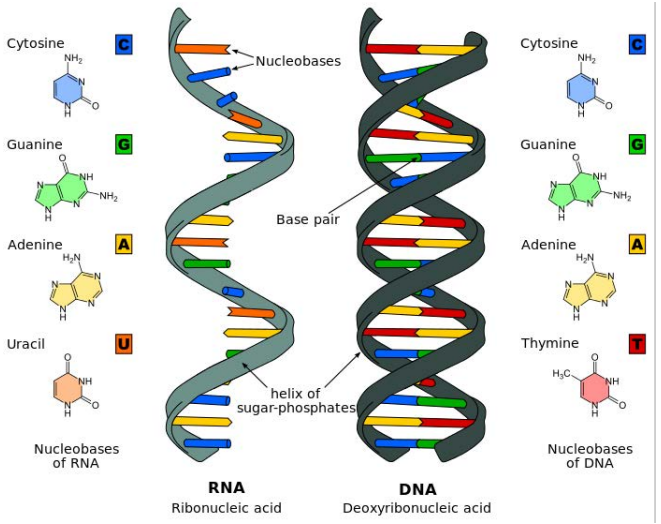
NUCLEOTIDES

Nucleotides: foundational to life

- Nucleotides are nutrients = food, or any nourishing substance assimilated by an organism, and required for growth, repair, and normal metabolism

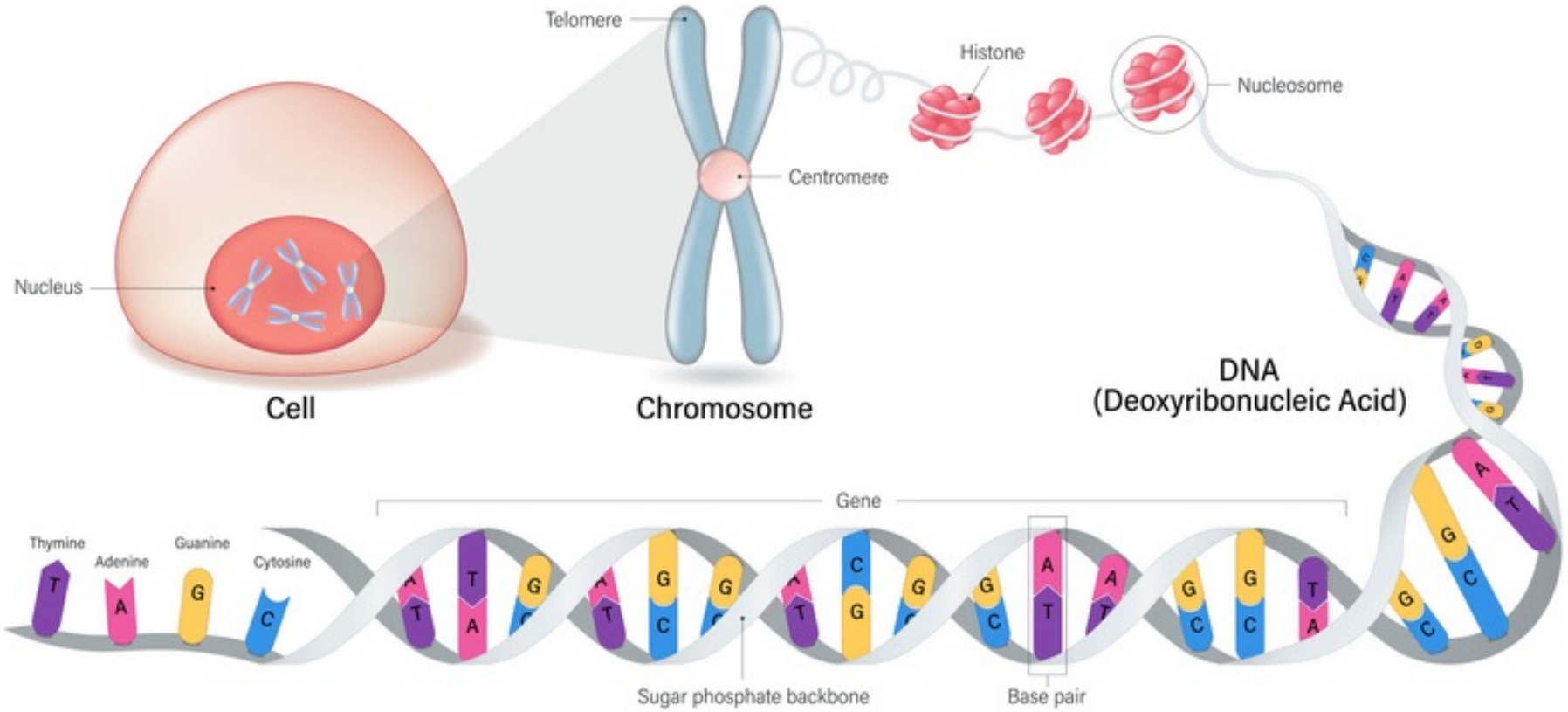
- Nucleotides are subunit molecules of RNA and DNA and therefore essential to life

  - 3 subunit molecules: a nucleobase, a five-carbon sugar (ribose or deoxyribose), 1 to 3 phosphate groups
  - Purine or pyrimidine bases
  - 3 sources: *de novo* synthesis, salvage and dietary consumption

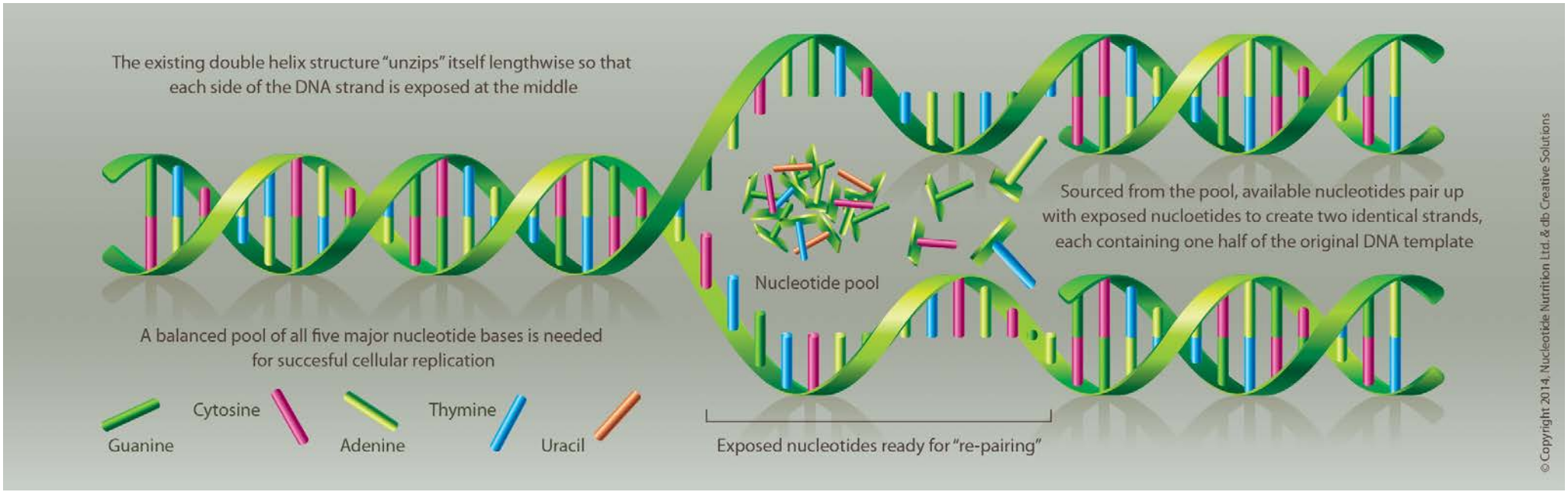


Purine bases: A, G
Pyrimidine bases: C, T/U

Nucleotides and DNA

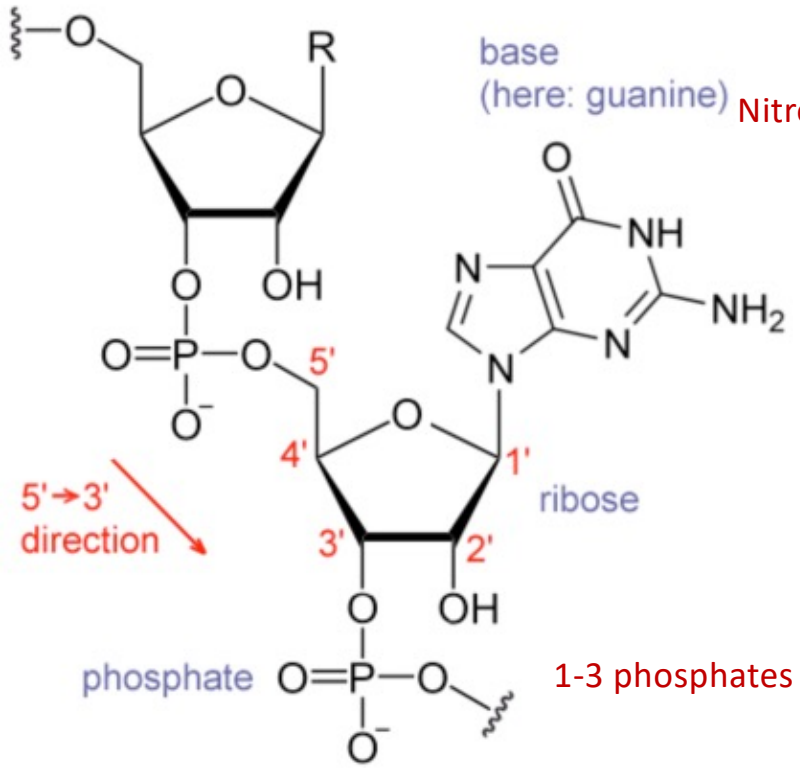


DNA replication → transcription → translation

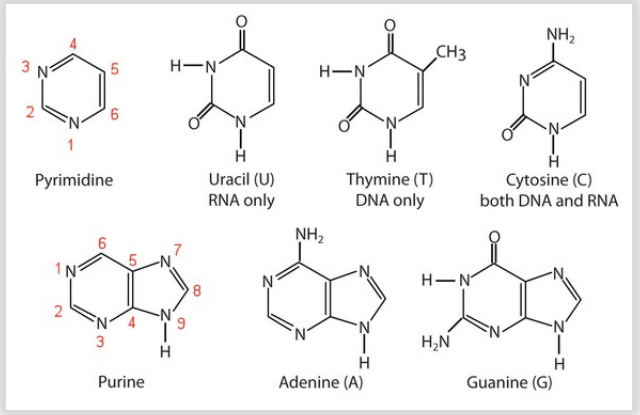


Nucleotides: molecular structure

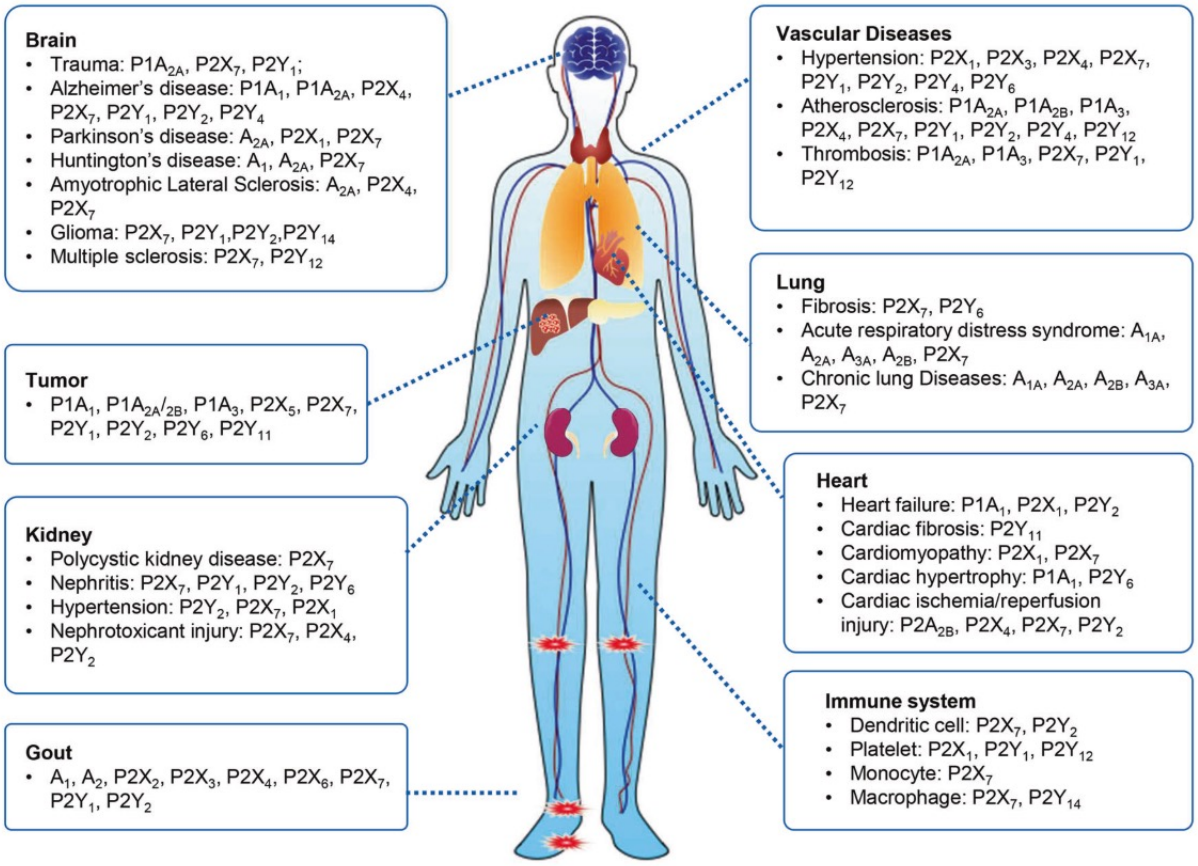
Pentose sugar (ribose or deoxyribose)



Classification according to nucleobase



Purinergic signalling – when it goes wrong…

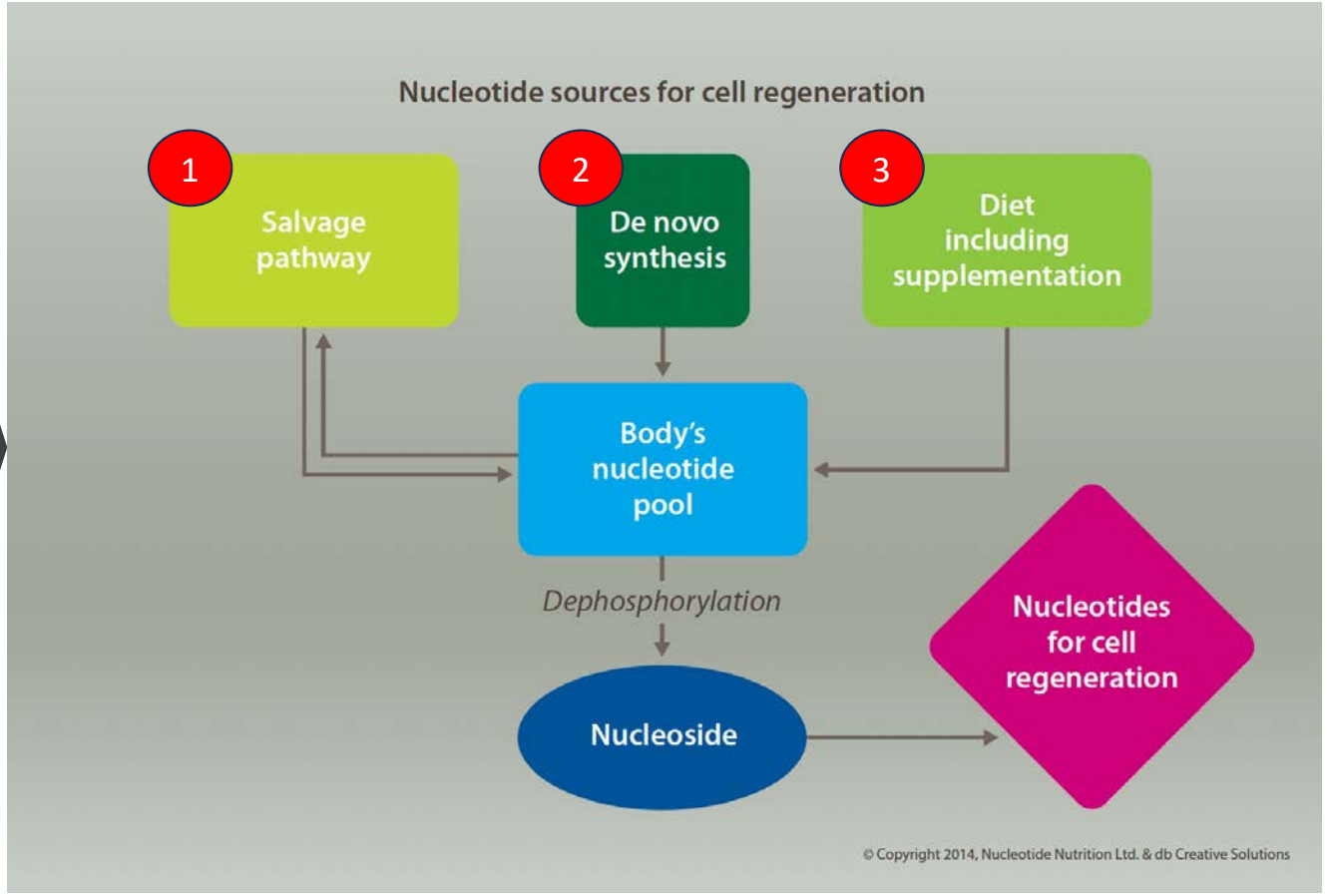


Huang, Z., Xie, N., Illes, P. et al. From purines to purinergic signalling: molecular functions and human diseases. *Sig Transduct Target Ther* 2021; 6: 162.

Origin of nucleotides

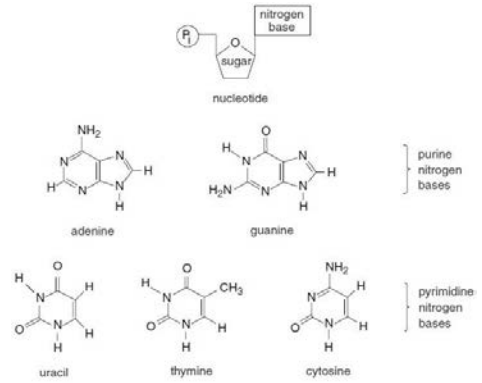
- Possibly among the first complex molecules to emerge in the 'primordial soup', according to the RNA World hypothesis
  Alberts B, Johnson A, Lewis J, et al. Molecular Biology of the Cell. 4th edition. New York: Garland Science; 2002. The RNA World and the Origins of Life.
- As components of nucleoproteins (e.g. nuclear DNA, chromosomes, histones, ribosomes), but also free
- Particularly rich in colostrum / breast milk
  Gil A. Modulation of the immune response mediated by dietary nucleotides. *Eur J Clin Nutr*. 2002; 56 Suppl 3:
  S1-4.
- Present in all foods, in highly variable quantities, notably meat (organs, offal), fish, fermented foods (e.g. tofu, natto, sauerkraut, Marmite), mushrooms, seeds
  Verkerk R. (2011) Nucleotides: Speculation on lifestyle-induced essentiality. *NHD Clinical*. 64:29-32

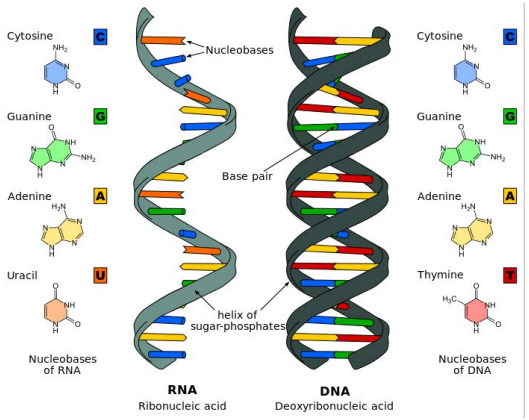
The three nucleotide sources for the body

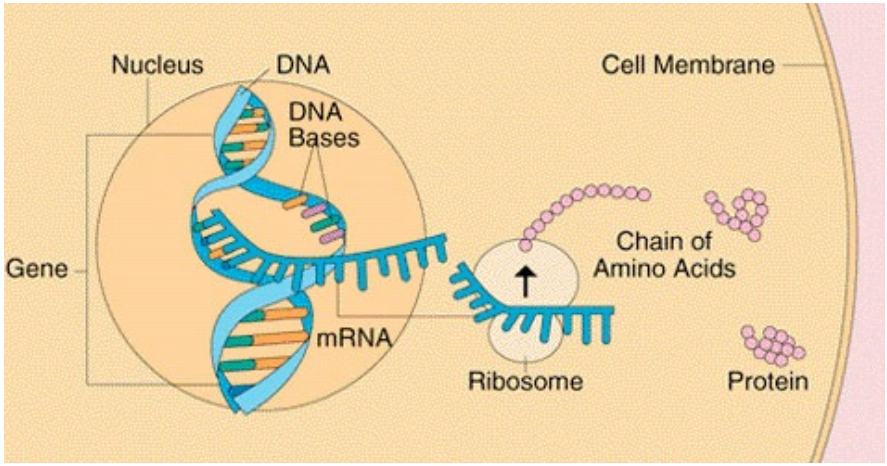


Key functions of nucleotides

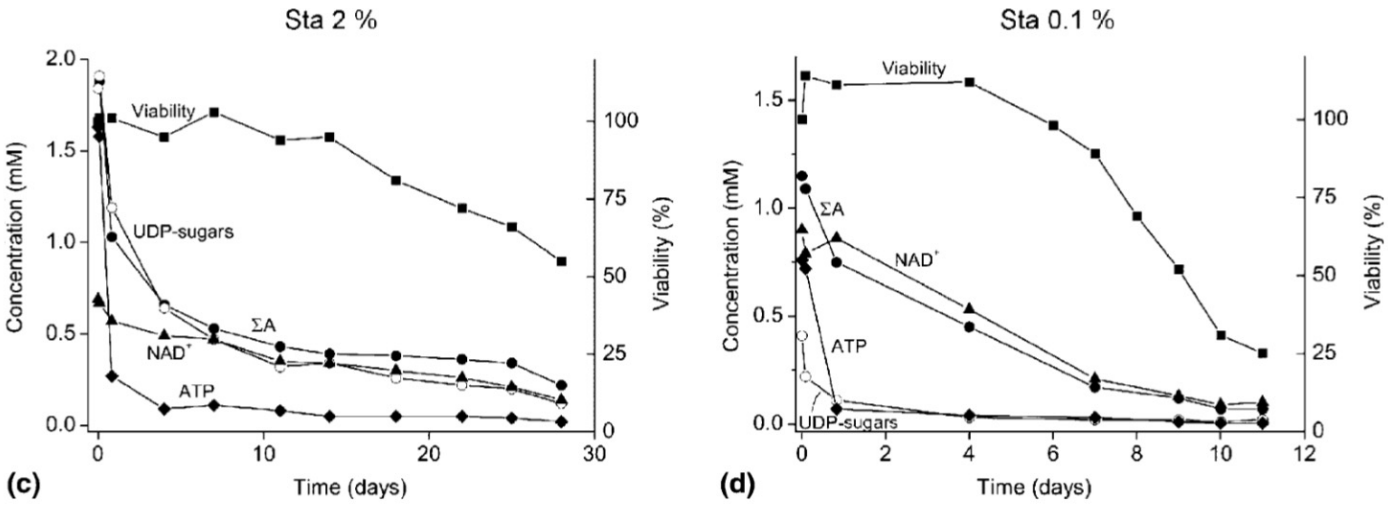
- Nucleic acid biosynthesis
- Energy production and transduction
- Protein biosynthesis
- Regulatory cascades
- İntra- and inter-cellular signal transduction
- Biosynthesis of biomolecules







Effect of stress on nucleotide synthesis (in yeast)



Osório et al. Influence of chronological aging on the survival and nucleotide content of Saccharomyces cerevisiae cells grown in different conditions: occurrence of a high concentration of UDP-N-acetylglucosamine in stationary cells grown in 2% glucose. *FEMS Yeast Research*, 2005; 5: 387–398.

Conditional essentiality of nucleotides

- Scientific consensus building, albeit slowly, post-Grimble (1993) over conditional essentiality of nucleotides

- Peak requirements:
  - rapid growth
  - infection, disease
  - stress, trauma

- Sites of requirement at times of peak requirement
  - immune system
  - GI system

- Insufficiency exacerbated by decreasing dietary intake of nucleotides

Grimble GK. Essential and conditionally-essential nutrients in clinical nutrition. *Nutr Res Rev.* 1993; 6(1): 97-119.

ESSENTIAL AND CONDITIONALLY-ESSENTIAL NUTRIENTS IN CLINICAL NUTRITION

GEORGE K. GRIMBLE

Department of Gastroenterology & Nutrition, Central Middlesex Hospital, Acton Lane, London NW10 7NS

CONTENTS

WHAT CONSTITUTES A CONDITIONALLY-ESSENTIAL NUTRIENT?

An essential nutrient can be defined as one whose absence from the diet will lead to growth impairment, organ dysfunction or failure to maintain nitrogen balance on an adequate intake of all other nutrients. This simple definition has proved useful in considering vitamin

Endogenous and exogenous sources

- *De novo* synthesis from metabolites such as glutamine, aspartate and glycine, particularly in the liver
- Salvage pathways, from RNA/DNA degradation
- Exogenous intake from diet

Source: Grimble GK, Westwood OM.
Curr Opin Clin Nutr Metab Care. 2001; 4(1): 57-64.

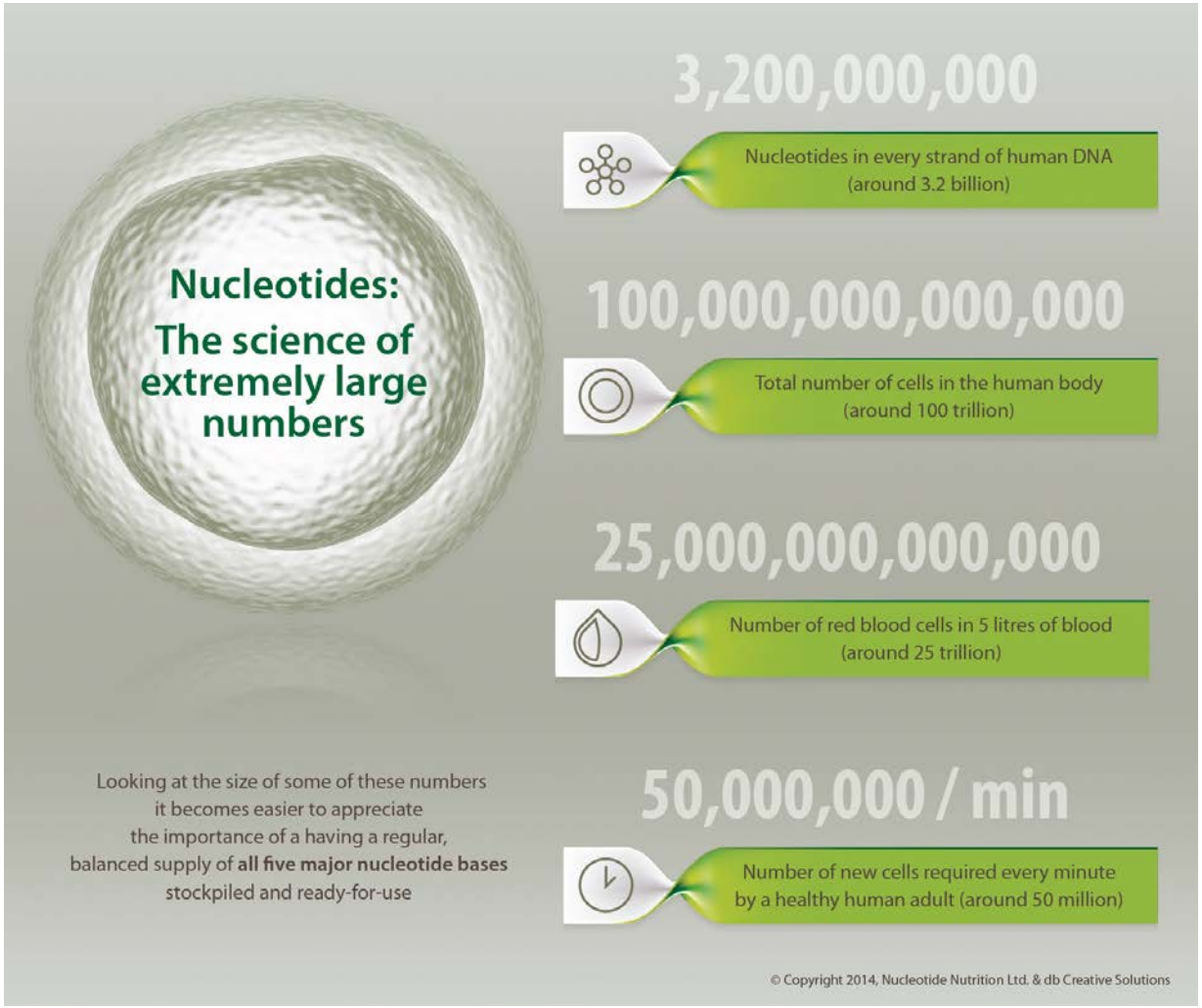
Nucleotides as immunomodulators in clinical nutrition

George K. Grimble and Olwyn M. Westwood

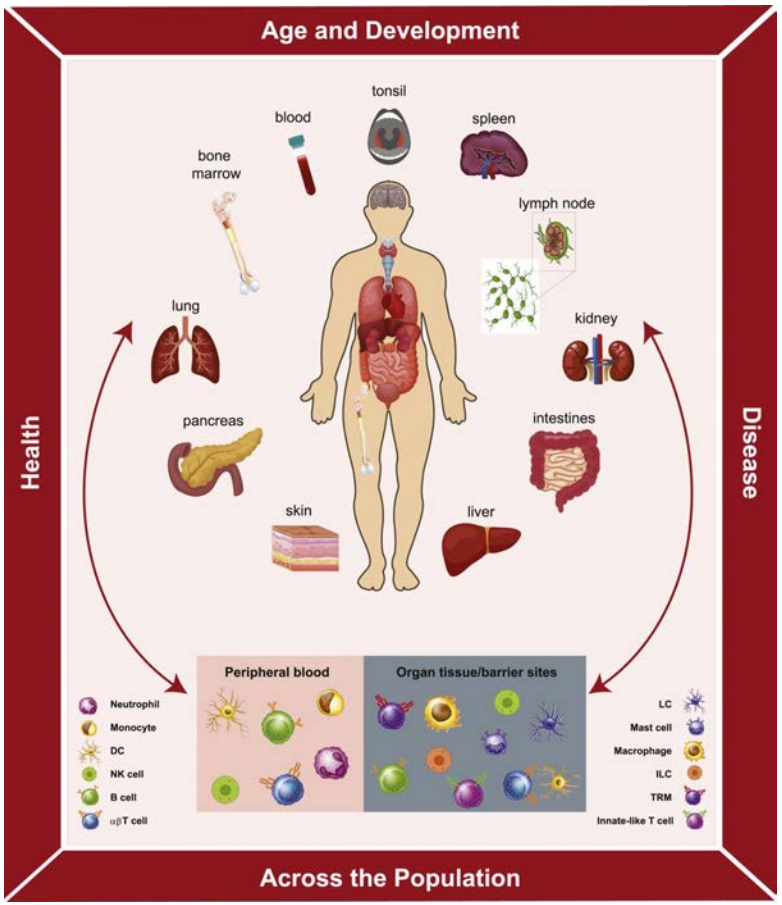
Dietary nucleotides, like glutamine, have attracted attention as a key ingredient missing from nutritional formulae for many years. They are the building blocks of tissue RNA and DNA and of ATP and their presence in breast milk has stimulated research in babies which has indicated that supplementation of infant formula milk leads to improved growth and reduced susceptibility to infection. Animal studies have confirmed some of these data. In particular, dietary nucleotides modulate immune function, promote faster intestinal healing and have trophic effects on the intestine of parenterally-fed rats which are similar to those resulting from glutamine supplementation, but at much lower intakes. Nucleotide supplementation has also been shown to improve some aspects of tissue recovery from ischaemia/reperfusion injury or radical resection. There is, however, a fundamental paradox. The intestine and liver possess powerful homeostatic mechanisms which degrade intake of purines and pyrimidines (ie salvage) and replace it with *de novo* synthesised output. It is possible that peripheral tissues receive only small amounts of nucleotides of dietary origin. Previously, nucleotides have been proposed as being conditionally-essential nutrients that provide an adequate supply of purines and pyrimidines for nucleic acid synthesis in neonates or in the stressed patient. This review explores this puzzle in the light of recent data from nutritional studies and from research into purinergic signalling in the intestine, heart and cells of the immune system. We propose that dietary nucleotides should be considered within a pharmacological and metabolic framework.

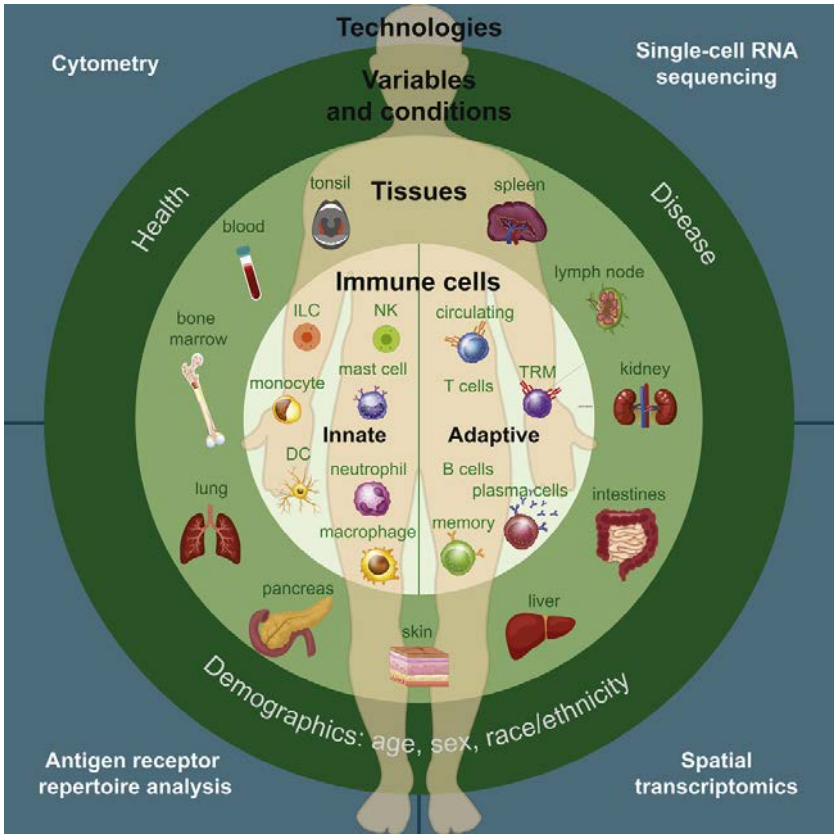
Curr Opin Clin Nutr Metab Care 3:000–000.

Nucleotides and big numbers



Nucleotides and the immune system





Poon MML, Farber DL. The Whole Body as the System in Systems Immunology. *iScience*. 2020; 23(9): 101509.

What was your nucleotide intake over the last 24 h?

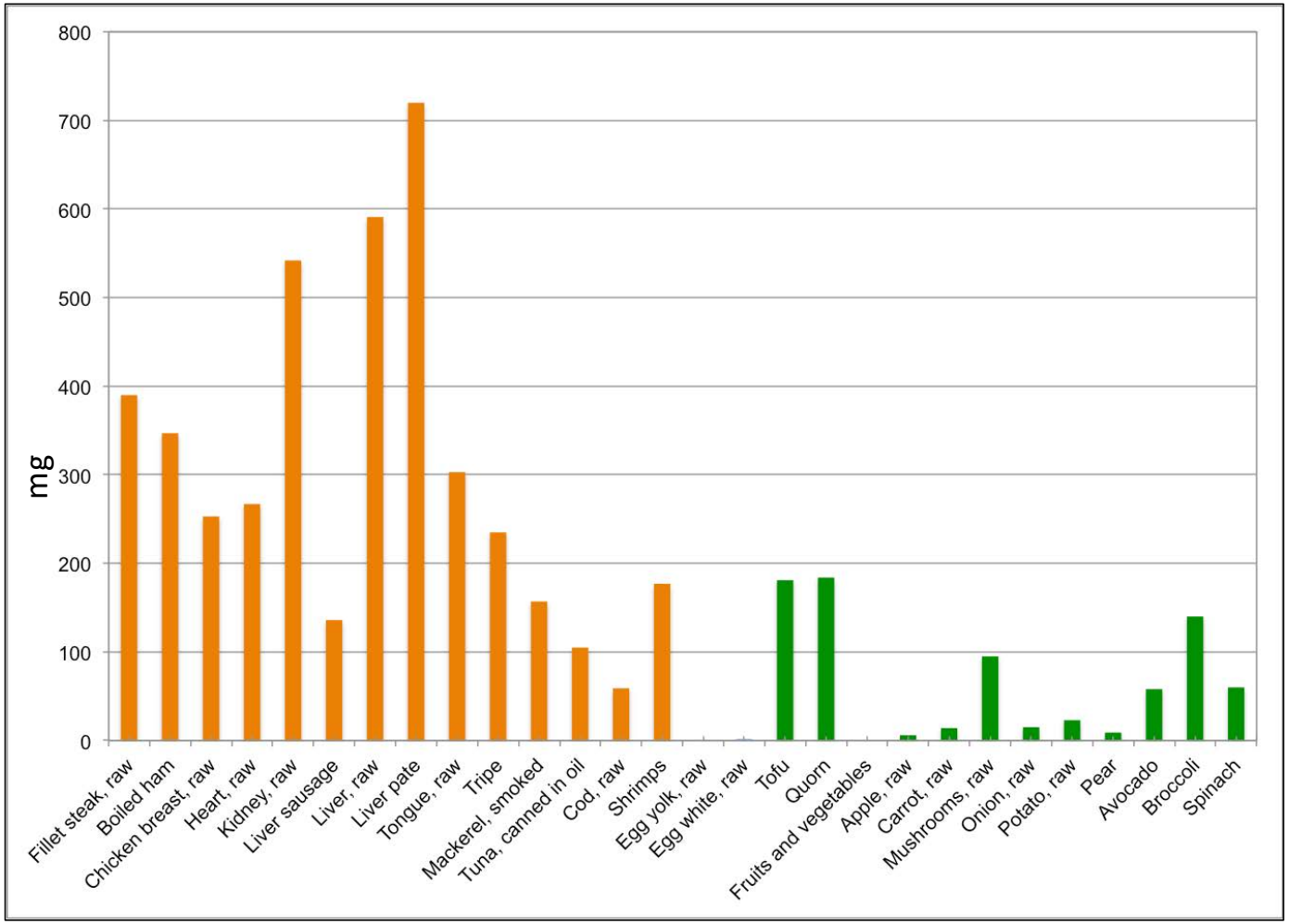
Nucleotide content of a typical conference buffet lunch

	Omnivore *(approx nucleotides in mg)*	**Vegan** *(approx nucleotides in mg)*
Antipasti 'meats'	300	–
Antipasti 'olives'	50	75
Tofu	100	200
Cheeses	50	–
Salad	20	25
Granary bread	15	15
Totals:	**535 mg**	**315 mg**

The approximate value of nucleotides (in mg) contained in an adult portion of each foodstuff available in a typical lunch buffet.
Sources: Dr. Robert Verkerk / ProBIO Switzerland

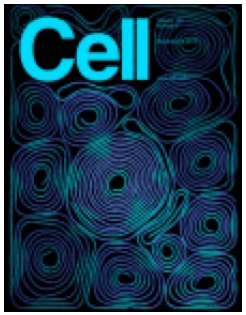
Nucleotides in the diet

Evaluation of total nucleotide content of a range of meat (orange) and vegetarian (green) protein sources according to typical single portions (analysis by Chemoforma/ProBio, produce purchased from supermarkets in Zurich, Switzerland).



Verkerk R. (2011) Nucleotides: Speculation on lifestyle-induced essentiality. *NHD Clinical*. 64:29-32

Relevance of low nucleotide pool



- A low-nucleotide pool in cells leads to DNA replication stress, inadequate DNA repair, genome instability, immune dysfunction and tumorigenicity

Bester et al. Nucleotide deficiency promotes genomic instability in early stages of cancer development. *Cell.* 2011;145(3):435-46.

Nucleotide Deficiency Promotes Genomic Instability in Early Stages of Cancer Development

Assaf C. Bester[1], **Maayan Roniger**[1], **Yifat S. Oren**[1], **Michael M. Im**[3], **Dan Sarni**[1], **Malka Chaoat**[2], **Aaron Bensimon**[4], **Gideon Zamir**[2], **Donna S. Shewach**[3], and **Batsheva Kerem**[1,*]

[1]Department of Genetics, The Life Sciences Institute, Edmond J. Safra Campus, The Hebrew University, Jerusalem 91905, Israel

[2]Department of Surgery, Hadassah Medical School, The Hebrew University, Jerusalem 91905, Israel

[3]Department of Pharmacology, University of Michigan Medical Center, Ann Arbor, MI 48109, USA

[4]Genomic Vision, 29 rue Faubourg Saint Jacques, 75014 Paris, France

SUMMARY

Chromosomal instability in early cancer stages is caused by stress on DNA replication. The molecular basis for replication perturbation in this context is currently unknown. We studied the replication dynamics in cells in which a regulator of S phase entry and cell proliferation, the Rb-E2F pathway, is aberrantly activated. Aberrant activation of this pathway by HPV-16 E6/E7 or cyclin E oncogenes significantly decreased the cellular nucleotide levels in the newly transformed cells. Exogenously supplied nucleosides rescued the replication stress and DNA damage and dramatically decreased oncogene-induced transformation. Increased transcription of nucleotide biosynthesis genes, mediated by expressing the transcription factor *c-myc*, increased the nucleotide pool and also rescued the replication-induced DNA damage. Our results suggest a model for early oncogenesis in which uncoordinated activation of factors regulating cell proliferation leads to insufficient nucleotides that fail to support normal replication and genome stability.

Key link to anti-ageing effects

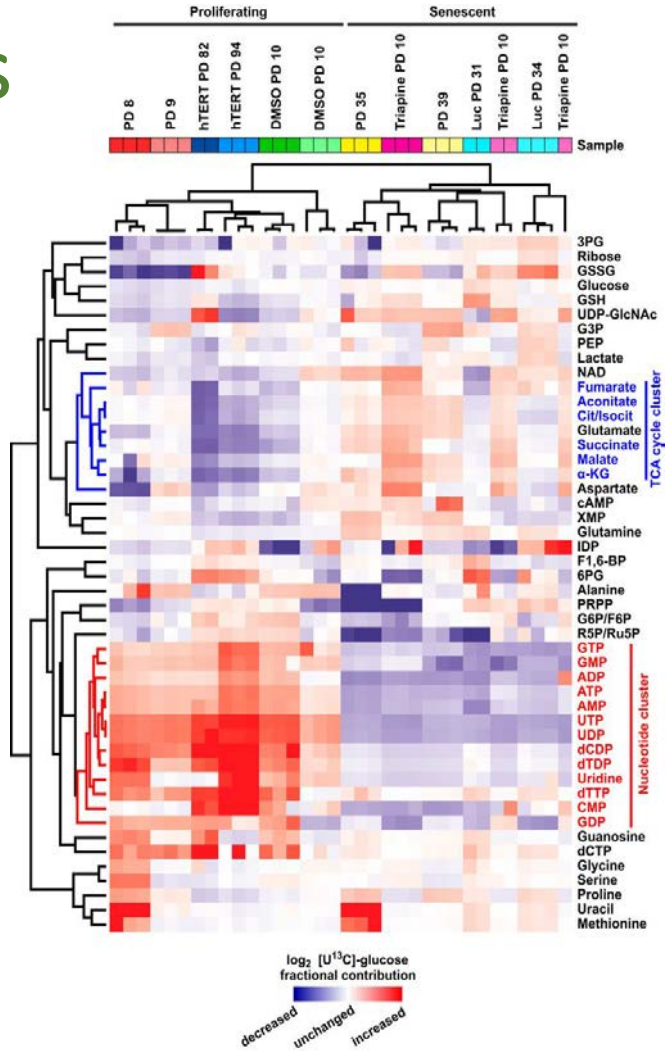
Inhibition of nucleotide synthesis promotes replicative senescence of human mammary epithelial cells

Received for publication, September 21, 2018, and in revised form, May 18, 2019 Published, Papers in Press, May 28, 2019, DOI 10.1074/jbc.RA118.005806

Alireza Delfarah[‡], Sydney Parrish[‡], Jason A. Junge[§], Jesse Yang[‡], Frances Seo[‡], Si Li[‡], John Mac[‡], Pin Wang[‡], Scott E. Fraser[§], and Nicholas A. Graham[‡¶1]

From the [‡]Mork Family Department of Chemical Engineering and Materials Science, the [§]Translational Imaging Center, Molecular and Computational Biology, and the [¶]Norris Comprehensive Cancer Center, University of Southern California, Los Angeles, California 90089

- Cellular senescence: cells have programmed number of cell divisions before they withdraw from the cell cycle in response to different stresses e.g. telomere shortening, DNA damage, or oncogenic signaling
- Inhibition of nucleotide synthesis causes early cell death (in human epithelial cell model)

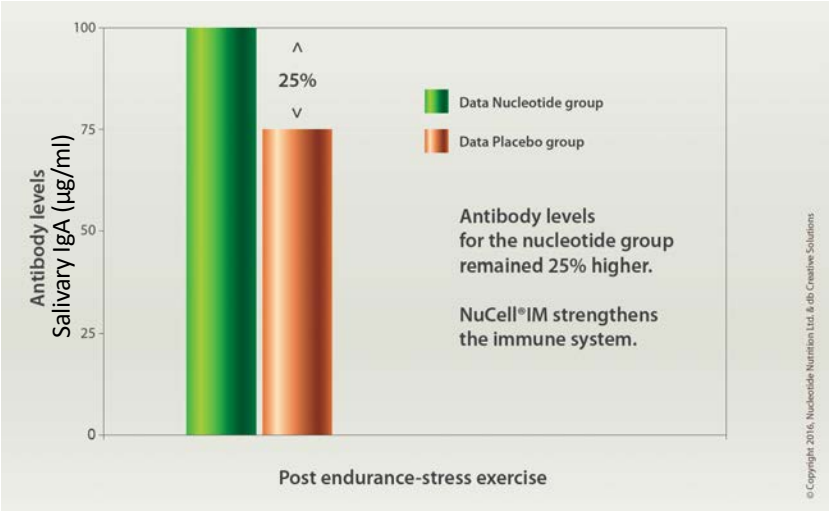


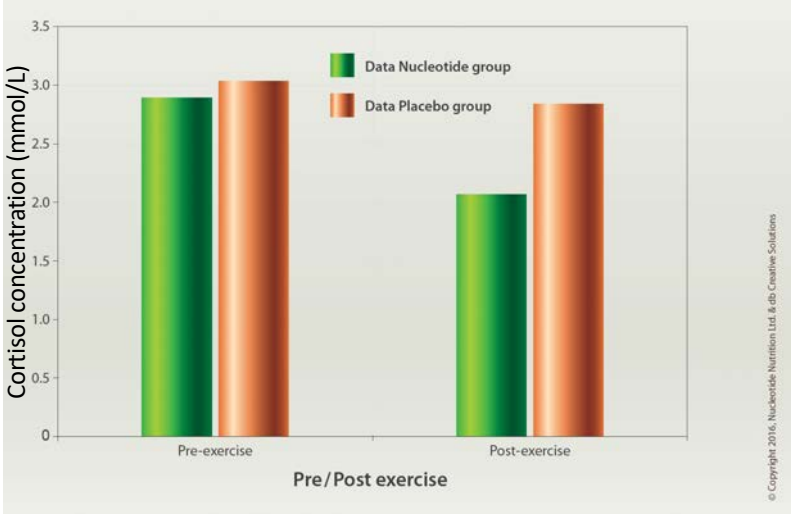
Source: Delfarah A et al. *J Biol Chem*. 2019 Jul 5; 294(27): 10564–10578.

Nucleotides, physical activity and immunity

Subjects 14, moderately trained male subjects. Age: 24.3 ± 3.6 y; weight: 79.4 ± 2.7 kg, height: 179.6 ± 4.2 cm. Incremental exercise test to exhaustion on a cycle ergometer to determine VO2max.

RCT: Lab endurance exercise trial (cycle ergometer): 90 min at a power output (W) @ 60% VO2max.





Mc Naughton L, Bentley D, Koeppel P. The effects of a nucleotide supplement on the immune and metabolic response to short term, high intensity exercise performance in trained male subjects. *J Sports Med Phys Fitness.* 2007; 47(1): 112-8.

Nucleotides and cancer [1]

Nucleotide Deficiency Promotes Genomic Instability in Early Stages of Cancer Development

Assaf C. Bester,[1] Maayan Roniger,[1] Yifat S. Oren,[1] Michael M. Im,[3] Dan Sarni,[1] Malka Chaoat,[2] Aaron Bensimon,[4] Gideon Zamir,[2] Donna S. Shewach,[3] and Batsheva Kerem[1,*]
[1]Department of Genetics, The Life Sciences Institute, Edmond J. Safra Campus
[2]Department of Surgery, Hadassah Medical School
The Hebrew University, Jerusalem 91905, Israel
[3]Department of Pharmacology, University of Michigan Medical Center, Ann Arbor, MI 48109, USA
[4]Genomic Vision, 29 rue Faubourg Saint Jacques, 75014 Paris, France
*Correspondence: kerem@cc.huji.ac.il
DOI 10.1016/j.cell.2011.03.044

Bester AC, et al. Nucleotide deficiency promotes genomic instability in early stages of cancer development. *Cell.* 2011;145(3):435-46.

nature metabolism
ARTICLES
https://doi.org/10.1038/s42255-020-0219-4
Check for updates

OPEN

Inosine is an alternative carbon source for CD8+-T-cell function under glucose restriction

Tingting Wang[1,8], J. N. Rashida Gnanaprakasam[1,8], Xuyong Chen[1], Siwen Kang[1], Xuequn Xu[1], Hua Sun[2], Lingling Liu[1], Hayley Rodgers[1], Ethan Miller[1], Teresa A. Cassel[3], Qiushi Sun[3], Sara Vicente-Muñoz[3], Marc O. Warmoes[3], Penghui Lin[3], Zayda Lizbeth Piedra-Quintero[4], Mireia Guerau-de-Arellano[4], Kevin A. Cassady[1], Song Guo Zheng[5], Jun Yang[6], Andrew N. Lane[3], Xiaotong Song[2,7]✉, Teresa W.-M. Fan[3]✉ and Ruoning Wang[1]✉

T cells undergo metabolic rewiring to meet their bioenergetic, biosynthetic and redox demands following antigen stimulation. To fulfil these needs, effector T cells must adapt to fluctuations in environmental nutrient levels at sites of infection and inflammation. Here, we show that effector T cells can utilize inosine, as an alternative substrate, to support cell growth and function in the absence of glucose in vitro. T cells metabolize inosine into hypoxanthine and phosphorylated ribose by purine nucleoside phosphorylase. We demonstrate that the ribose subunit of inosine can enter into central metabolic pathways to provide ATP and biosynthetic precursors, and that cancer cells display diverse capacities to utilize inosine as a carbon source. Moreover, the supplementation with inosine enhances the anti-tumour efficacy of immune checkpoint blockade and adoptive T-cell transfer in solid tumours that are defective in metabolizing inosine, reflecting the capability of inosine to relieve tumour-imposed metabolic restrictions on T cells.

Wang T, et al. Inosine is an alternative carbon source for CD8+-T-cell function under glucose restriction. *Nat Metab.* 2020;2(7):635-647.

Nucleotides and cancer [2]

www.aging-us.com AGING 2021, Vol. 13, No. 9

Review

Emerging roles of nucleotide metabolism in cancer development: progress and prospect

Jingsong Ma[1,2], Mengya Zhong[1,2], Yubo Xiong[1,2], Zhi Gao[3], Zhengxin Wu[4], Yu Liu[5], Xuehui Hong[1,2]

[1]Institute of Gastrointestinal Oncology, School of Medicine, Xiamen University, Fujian, Xiamen 361000, China
[2]Department of Gastrointestinal Surgery, Zhongshan Hospital, Xiamen University, Fujian, Xiamen 361000, China
[3]National Center for International Research of Biological Targeting Diagnosis and Therapy, Guangxi Key Laboratory of Biological Targeting Diagnosis and Therapy Research, Guangxi Medical University, Guangxi, Nanning 53000, China
[4]Medical College of Guangxi University, Guangxi, Nanning 530000, China
[5]General Surgery Center, Bazhong Central Hospital, Sichuan, Bazhong 636000, China

Correspondence to: Xuehui Hong; **email:** hongxu@xmu.edu.cn
Keywords: nucleotide metabolism, tumor immunity, key metabolic enzyme, signaling pathway, oncogene-induced senescence
Received: August 12, 2020 **Accepted:** March 29, 2021 **Published:** May 5, 2021

ABSTRACT

Abnormal cancer metabolism occurs throughout the development of tumors. Recent studies have shown that abnormal nucleotide metabolism not only accelerates the development of tumors but also inhibits the normal immune response in the tumor microenvironment. Although few relevant experiments and reports are available, study of the interaction between nucleotide metabolism and cancer development is rapidly developing. The intervention, alteration or regulation of molecular mechanisms related to abnormal nucleotide metabolism in tumor cells has become a new idea and strategy for the treatment of tumors and prevention of recurrence and metastasis. Determining how nucleotide metabolism regulates the occurrence and progression of tumors still needs long-term and extensive research and exploration.

Clinical recommendations

High dietary requirement is key under the following conditions:

- Immune compromised/challenged
- Gut dysbiosis/permeability, IBS, IBD, etc.
- Physical stress, intense exercise, sleep deprivation
- Psycho-emotional stress

Primary support: gut, microbiome and immune system:

- Food: organ meats, offal, fish, fermented foods, mushrooms – *quantis satis*
- Supplements: 1-10 g of purine/pyrimidine balanced purified extracts daily, depending on need, condition, immunological status, stress, etc.

PEPTIDE BIOREGULATORS

Peptides: what are they?

Definition

- A peptide is a short string of 2 to 50 amino acids, formed by a condensation reaction, joining together through a covalent bond.

- >20 AAs in unbranched chain = polypeptide

Effects

Antibacterial, antitumor, anti-inflammatory and antioxidant activities, involved in the regulation of neuro-immuno-endocrine system, digestive processes, appetite and blood pressure and having analgesic and anti-ageing, pancreo- and nephro-bronchoprotective effects

Bioactive peptides

- plant peptides
- bacterial/antibiotic peptides
- fungal peptides
- invertebrate peptides
- amphibian/skin peptides
- venom peptides,
- cancer/anticancer peptides
- vaccine peptides
- immune/inflammatory peptides
- brain peptides
- endocrine peptides
- ingestive peptides
- gastrointestinal peptides
- cardiovascular peptides
- renal peptides
- respiratory peptides
- opioid peptides
- neurotrophic peptides
- blood–brain peptides

Abba J. Kastin, ed. (2013). Handbook of Biologically Active Peptides (2nd ed.). Elsevier Science.
Forbes J, Krishnamurthy K. Biochemistry, Peptide. [Updated 2023 Aug 28]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing.
Kolchina N, et al. Systematic search for structural motifs of peptide binding to double-stranded DNA. Nucleic Acids Res. 2019; 47(20): 10553-10563.

Bioregulatory peptides: key issues for research

- How are they produced? Ribosomal vs non-ribosomal synthesis
- What cells, tissues and organs produce regulatory peptides?
- How are regulatory peptides transported through barriers (cell membrane, intestinal membrane, blood/brain barrier, nuclear membrane)?
- What is the mode of action of regulatory peptides with target cells/tissues/organs?

Regulatory peptides: status of current knowledge

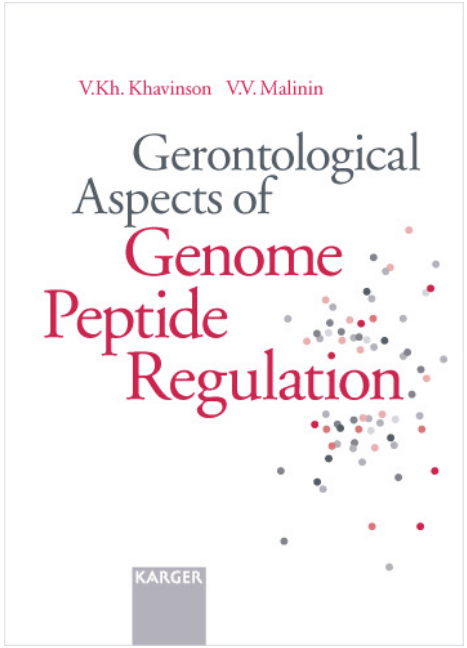
Vladimir Khavinson PhD
7 Nov 1946 – 6 Jan 2024

- Short peptides (2–7 amino acid residues) can penetrate into the nuclei and nucleoli of cells and interact with the nucleosome, the histone proteins, and both single- and double-stranded DNA.
- DNA–peptide interactions, including sequence recognition in gene promoters, are important for template-directed synthetic reactions, replication, transcription, and DNA repair.
- Peptides can regulate the status of DNA methylation, which is an epigenetic mechanism for the activation or repression of genes in both the normal condition, as well as in cases of pathology and senescence.
- Short peptides were evolutionarily among the first signaling molecules that regulated the reactions of template-directed syntheses.
- Basis for effective and safe immunoregulatory, neuroprotective, antimicrobial, antiviral, and other bioregulatory processes.

Khavinson VK, Popovich IG, Linkova NS, Mironova ES, Ilina AR. Peptide Regulation of Gene Expression: A Systematic Review. Molecules. 2021; 26(22): 7053.

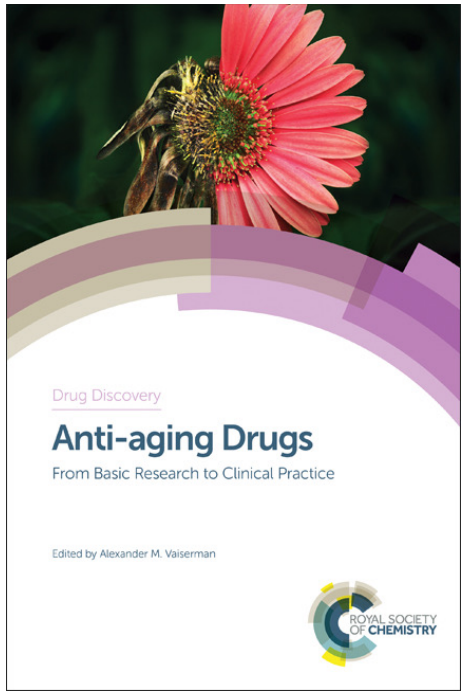
Regulation of gene expression, protein synthesis, immune modulation, enhancement of life span, etc.....

The future of medicine?



Khavinson V, Malinin VV. Gerontological Aspects of Genome Peptide Regulation. 2005. Basel (Switzerland): Karger AG. 104 pp.

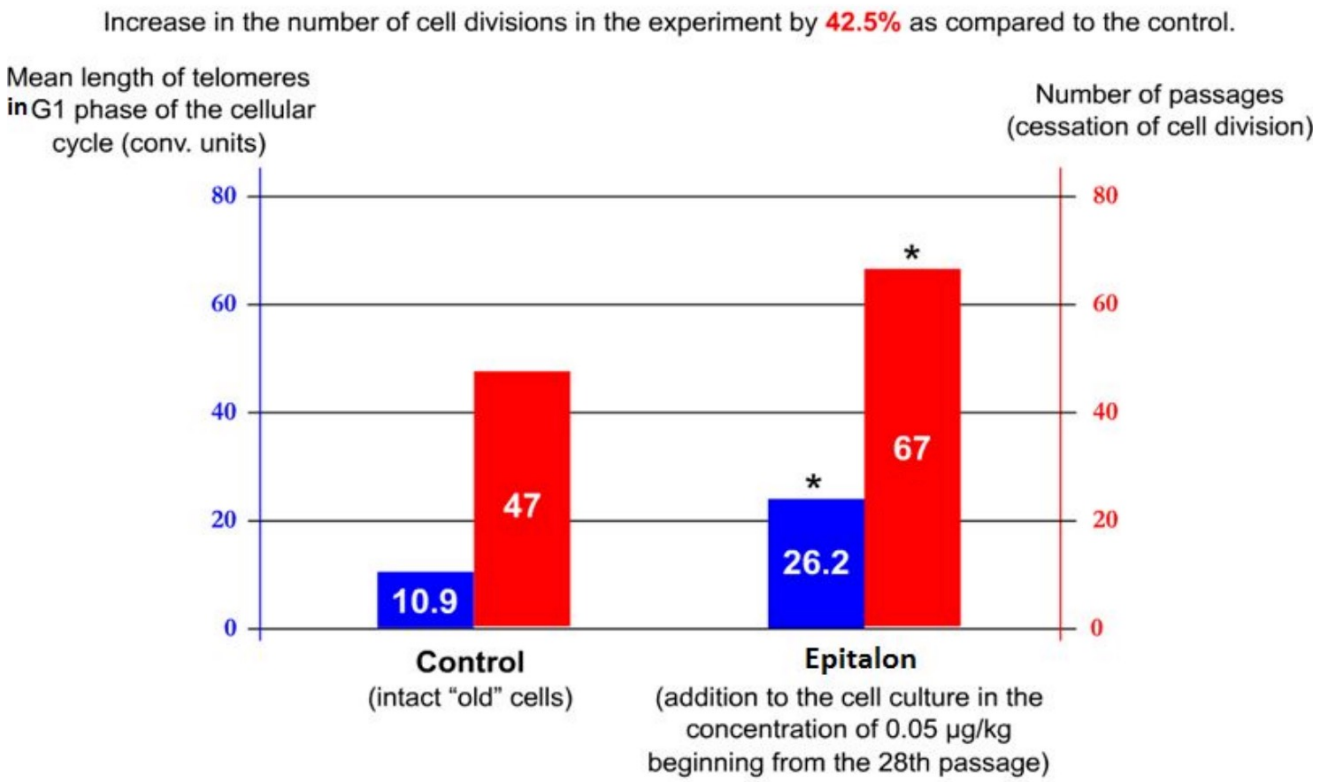
Khavinson V. Peptides and Ageing. *Neuro Endocrinol Lett.* 2002 Jan; 23(Suppl 3): 11-144



Khavinson V, Popovich, I. Short Peptides Regulate Gene Expression, Protein Synthesis and Enhance Life Span. RSC Drug Discovery Series No. 57. Anti-aging Drugs: From Basic Research to Clinical Practice, Ed. Alexander M. Vaiserman. 2017. Chapter 20, pp. 496-513.

Also: https://khavinson.info/publications

Peptides – counteracting immunosenescence



Khavinson VKh, Anisimov VN. Peptide regulation of aging: 35-year research experience. *Bull Exp Biol Med.* 2009; 148(1): 94-8.

Bill Lawrence JD PhD: USA

Peptide Bioregulators - interview with Bill Lawrence PhD

8.6K views • 10 months ago

Johnny Adams

Bill describes the **peptide** bioregulator research program.

Dr Bill Lawrence Khavinson Peptide Bioregulators Q&A

293 views • 3 weeks ago

Johnny Adams

Dr Bill Lawrence answers questions about Khavinson **Peptide** Bioregulators FIRST watch the original recording here: ...

Peptide Bioregulators To Slow Biological Aging & Increase Telomeres - Dr Bill Lawrence

5.2K views • 1 year ago

Hack My Age

Researcher **Dr. Bill Lawrence** shares his discoveries of aging and telomeres in his clinical trials over the last 4 years. We learn ...

Introduction | Clinical Studies Collaboration | Collaboration on Aging Research | Peptide... 17 chapters

TruDiagnostic™
The Epigenetic Company

DISCOVER YOUR

biological age, risk of death & disease, and so much more- from 75+ epigenetic biomarkers!

We have two testing options to help wellness and anti-aging enthusiast understand their body's aging processes on a cellular level.

Peptide bioregulators

Pineal Bioregulator

View Product

Prostate Bioregulator

View Product

Retina Bioregulator

View Product

Stomach Bioregulator

View Product

Testes Bioregulator

View Product

Thymus Bioregulator

View Product

Thyroid Bioregulator

View Product

Lungs Bioregulator

View Product

Muscle Bioregulator

View Product

naturesmarvels.com/products/

Clinical recommendations

- Take no more than 5 different peptide bioregulators concurrently
- Take up to 2 capsules, 3x daily
- Take for 1-2 months pa

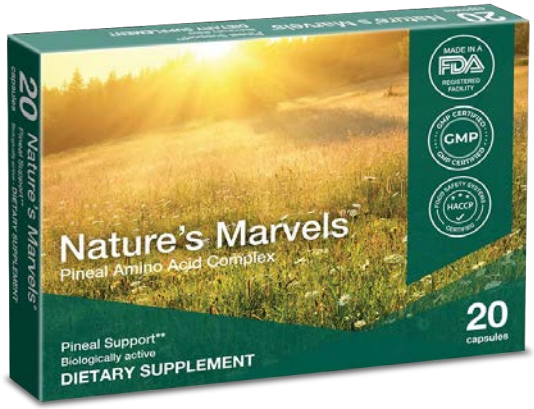
For further information:
naturesmarvels.com

This table presents which bioregulators can be taken in conjunction, it also shows which bioregulators can be taken for a health condition or body system.

Health Condition / Concern / Body System

Peptide Bioregulator	Carbohydrate Metabolism / Glycaemic Control	Digestive System	Central Nervous System / Cognitive	Cardio-Vascular System	Upoprotein Metabolism	Thyroid	Immune System	Locomotion Cartilage / Joint	Male Reproductive	Female Reproductive	Urinary Excretory System	Respiratory	Visual	Ionizing Radiation / Chemo-therapy	Psycho-emotional stress	Intensive Physical Activity Support
Vessels / Vascular	✓		✓	✓	✓	✓	✓	✓		✓		✓	✓			✓
Thymus / Immune				✓			✓	✓			✓	✓		✓	✓	✓
Brain / CNS			✓										✓			✓
Kidney											✓					
Cartilage / Joints / Bone								✓								✓
Liver / Digestive	✓	✓	✓		✓									✓		
Thyroid						✓				✓						
Pancreas / Glycaemic	✓	✓			✓											
Pineal / Neuroendocrine			✓				✓							✓	✓	
Bladder											✓					
Testes / Reproductive									✓							
Heart				✓												
Adrenal									✓						✓	
Bone Marrow / Hemopaletic														✓		
Stomach		✓														
Eye / Visual													✓			
Ovaries / Reproductive										✓						
Prostate									✓							
Muscle																✓
Bronchi / Respiratory												✓				
Parathyroid / Bone								✓								

Regimens



- **Standard regimen**

  Begin with an 'intensive course' of 2-capsules every day for 30-days (60 capsules in total) and to then proceed each additional month at 2-capsules each day for 10-days (that's 20 capsules in-total) e.g. last 10-days of the month that follows the end of the intensive course.

- **Intensive regimen**

  A small proportion of people with special requirements may benefit from doubling the daily dosages given above, i.e. 2 capsules daily for 30 days, and pulsed dosing thereafter, as required, at 2 capsules twice daily for 10 days each month.

- **Maintenance regimen**

  20 capsules every three months i.e. 2 capsules twice a day for 10-days.

REGULATORY AWARENESS

Regulator & drug company scrutiny

WIKIPEDIA
The Free Encyclopedia

Epitalon is a synthetic peptide, telomerase activator, and putative anti-aging compound,[1][2] which was identified as the putative active component of a bovine pineal gland extract known as **epithalamin**.[3]

Most studies on epitalon and epithalamin have been conducted by the St. Petersburg Institute of Bioregulation and Gerontology, primarily overseen by Vladimir Khavinson, in Russia.[2][4][5][6][7]

Chemistry [edit]

Epitalon is a tetrapeptide with the amino acid sequence Ala-Glu-Asp-Gly and the molecular formula $C_{14}H_{22}N_4O_9$.[8]

FDA

Epitalon	503A	September 29, 2023	Compounded drugs containing epitalon may pose risk for immunogenicity for certain routes of administration due to the potential for aggregation and peptide-related impurities. FDA has not identified safety-related information regarding epitalon for the proposed route of administration; thus, we lack sufficient information to know whether the drug would cause harm if administered to humans.

Source: www.fda.gov/drugs/human-drug-compounding/safety-risks-associated-certain-bulk-drug-substances-nominated-use-compounding

Food supplements

1. Normally consumed in diet
2. Not a novel food ingredient
3. Dosage within normal physiological range
4. Not significantly active pharmacologically, immunologically or metabolically
5. “Clearly” a food or food supplement ingredient


1
Not presented as treating or preventing disease
2
All claims must be substantiated
3
Only authorised health claims can be made
4
Non-authorised health claims cannot be made
5
Clinical studies on disease conditions cannot be used
Claims

Prescription of unregistered medicines

A Member State may, in accordance with legislation in force and to fulfil special needs, exclude from the provisions of this Directive medicinal products supplied in response to a bona fide unsolicited order, formulated in accordance with the specifications of an authorised health-care professional and for use by an individual patient under his direct personal responsibility.

Article 5(1), Directive 2001/83/EC, as amended

‘Biosimilars’, modified/synthetic natural products, engineered nanomaterials

Biosimilar (natural or synthetic)	Pharmacological action/claim	Unauthorised drug
Natural product	Post-05/97 structural alteration, new process	Unauthorised novel food
Nanomaterial (<100 nm)	Engineered	Non-authorised novel food

Syn peptides/oligopeptides

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 September 2022
EMA/CHMP/QWP/735422/2022
Committee for Medicinal Products for Human Use (CHMP)
Committee for Veterinary Medicinal Products (CVMP)

Concept Paper on the Establishment of a Guideline on the Development and Manufacture of Synthetic Peptides

Agreed by Quality Working Party	29 June 2022
Adopted by CHMP for release for consultation	15 September 2022
Adopted by CVMP for release for consultation	8 September 2022
Start of public consultation	20 September 2022
End of consultation (deadline for comments)	20 December 2022

Comments should be provided using this template. The completed comments form should be sent to QWP@ema.europa.eu

Keywords	Guideline, Chemistry, Development and Manufacture, Drug Substance, New Active Substance, Synthetic Peptides

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

15 September 2022
EMA/CHMP/QWP/735423/2022
Committee for Medicinal Products for Human Use (CHMP)
Committee for Veterinary Medicinal Products (CVMP)

Concept Paper on the Establishment of a Guideline on the Development and Manufacture of Synthetic Oligonucleotides

Agreed by Quality Working Party	29 June 2022
Adopted by CHMP for release for consultation	15 September 2022
Adopted by CVMP for release for consultation	8 September 2022
Start of public consultation	20 September 2022
End of consultation (deadline for comments)	20 December 2022

Comments should be provided using this template. The completed comments form should be sent to QWP@ema.europa.eu

Keywords	Guideline, Chemistry, Development and Manufacture, Drug Substance, New Active Substance, Synthetic Oligonucleotides

Take-homes

- Nucleotides and peptides are vital for gene expression, cell signaling, cell cycle, immune function and lifespan
- Can be found in diet or produced de novo, but not under conditions of stress or disease
- Supplemental intakes can be key in re-establishing homeostatic function
- Quality sources are essential


HELPING TO CREATE HEALTH.
WORKING WITH NATURE, NOT AGAINST IT.
alliance for natural health INTERNATIONAL
alliance for natural health USA
Thank you.
anhintl
ANHInternational
@anhcampaign
anhinternational.org
anh-usa.org