

## Appendix 1

*Cell/molecular biological Goldilocks zones*

- The level of the signal molecule mTOR which ensures proper functioning of the anti-tumour agent *Treg* in immune cells: Zeng (2017) –
- Appropriate proximity to the ‘niche’ environment in the crypt region of the colon in order to ensure the persistence of stem cell potential: Walther and Graham (2014)
- The need for microbial communities to be neither too distant nor too close for high levels of emergent biosynthetic capacity to occur (Chiu et al 2014)
- The need to maintain a balance in the expression, activation and repression of Pattern Recognition Receptors in order to promote immune system homeostasis in the GI tract: (Ringel-Scala et al 2016)
- An appropriate balance of the highly gene-dosage-sensitive Notch pathway, a fundamental signalling mechanism required for differentiation and tissue homeostasis; too much or too little can lead to disease. (Braune and Lendahl 2016)
- ‘Goldilocks’, is the name applied to the Python computer package which takes a census of gene sequence data to identify genomic regions which are ‘just right’ (Nicholls et al, 2013)
- Mechanoresponsive proteins have Goldilocks zones of actin binding affinity in order to carry out cytoskeleton reorganisation in response to changing mechanical environments. (Schiffhauer et al 2015)
- Understanding *Mycobacterium tuberculosis* infection requires information on the balance of key chemokines/cytokines and their receptors and how loss of that balance can promote disease (Domingo-Gonzalez et al 2016).
- The ideal ‘Goldilocks’ Chemistry allows DNA and RNA to carry out their fundamental function in molecular heredity (Houlihan et al 2017)
- An allosteric Serine- Arginine protein -phosphatase platform which balances phosphorylation levels in a ‘goldilocks region’ is required for the proper sub-nuclear stage of a protein kinase protein splicing factor (Aubot et al 2017)
- Methyl-CpG-binding protein (MeCP2) must stay within a narrow range of expression – not too much, not too little – to be functionally ‘just right’ for proper epigenetic regulation in order to limit devastating phenotypic outcomes (immune defects underlying neurological deficits) (Boothby and Williams, 2012)
- Undifferentiated Embryonic Cell Transcription Factor (Utf1) ensures that conditions are precisely right for maintaining pluripotency and self-renewal in embryonic stem cells (Laskowski and Knoepfler 2012)

*Tissue/whole body biology applied in medicine Goldilocks zones*

- To minimise the risk of bone fractures, vitamin D levels need to be between 'lower' and 'higher', both of which increase the risk (Baughman and Lower 2014)
- A high and low proportion of carbohydrate in the diet is associated with increased human mortality, with minimal risk at 50-55% carbohydrate intake (Seidelmann et al 2018)
- Appropriate redox balance in striated muscle, where ROS production is counterbalanced by antioxidant capacity requires a Goldilocks zone, which scales down from the whole tissue to mitochondrial level: Alleman et al 2014)
- Optimal development of advanced therapeutic medicinal products for bone repair need to be neither too simple nor too complex (Leijten et al 2015)
- Appropriate timing, dose and regimen of estrogen exposure is required to promote beneficial effects on cognition (Koebele and Bimonte-Nelson, 2015)
- Vitamin C concentrations which are 'just right' (especially not unphysiologically high) are needed in order to interpret effects of the vitamin on human physiology (Padayatty and Levine, 2016)
- Recommendations for post-polypectomy surveillance should aim to target a Goldilocks zone (Ladabaum and Schoen, 2016)
- The need to balance fetal needs vs maternal supply during pregnancy in great apes and humans in terms of the level of inflammation; is essential during implantation; otherwise there is the risk of disorders such as gestational diabetes and choriodecidual inflammatory syndrome (Clancy, 2013).
- With regard to fluid management around the time of surgery – too little (pre- and post- operatively) is associated with inadequate organ perfusion and too much, with tissue oedema and surgical complications. Finding the 'Goldilocksian' 'just right' zone is the challenge (Cuthbertson, 2013).
- Judicious surgery for breast cancer indicates that a 2mm margin is superior to a narrower one in patients with Ductal Carcinoma In Situ and that bigger is not necessarily better (Jagsi 2016)
- Networks of neurones need to stay in a Goldilocks zone between 'too quiet' and 'too active' (Humphries 2016).
- The 'Goldilocks zone' of fatty acid metabolism is required to ensure that the relationship with cardiac function is just right. (Kerr et al 2017).

- In emergency medicine a balance needs to be struck between the speed of treatment and its accuracy – sicker patients are more likely to benefit from intervention whereas less sick do not and may be harmed. It is necessary to get into the *Goldilocks zone*; the ‘just right’ balance between speed and accuracy (Fatovich, 2017)
- In the use of exercise to maintain joint homeostasis in the horse, too little or too much can result in joint derangement whereas just the right amount will provide optimal functioning of the joint (Milner 2017).
- In the treatment of perioperative blood pressure, the anaesthetist should aim at the ‘Goldilocks’ range, reminiscent of the optimal haemoglobin concentration, and avoid excursions in either direction (Sweitzer and Howell, 2017)
- ‘Goldilocks’ software is used in facilitating hearing-aid self-fitting *to allow user exploration and selection of preferred levels of overall output, low-frequency cut and high frequency boost.* (Boothroyd et al 2017).
- In the administration of oxygen in the clinical situation, the move is to avoid both excessive and inadequate therapy – moving away from the notion that more is always better and instead giving the least amount necessary (Martin and Grocott 2017).
- A ‘Goldilocks trial design’ constantly asks *‘Is the sample size too big, too small or just right?’* As an example, Broglio et al (2014) present a Bayesian adaptive design for a confirmatory trial to select a trial’s sample size based on accumulating data
- The Goldilocks dilemma in acute ischemic stroke asks which patients are ‘just right’ for endovascular treatments (Tansy and Liebeskind 2013)
- Excess or deficiency of retinoic acid leads to inner ear dysmorphogenesis via an effect on FGF3/1/2/10 signalling; referred to as a Goldilocks phenomenon (Frenz et al 2010)
- For patients with newly diagnosed glioblastoma, the goal is to define the ‘Goldilocks zone’ for the optimal duration of adjuvant temozolomide (Grossman and Keleinberg 2017)
- Following lung injury, different progenitor cell populations can arise depending on the molecular environment – resulting in normal or aberrant alveolar repair. A key question is how to maintain a ‘Goldilocks zone’ of repair (Dean and Lloyd 2017) – nice diagram
- The design of inferior vena cava filters for the treatment of Venous thromboembolic disease relies on a ‘Goldilocks’ premise: i.e., make the device stable, (so it doesn’t migrate) but not too stable (so you can still retrieve it) (Magnowski et al 2017)

- Genetic variation in humans occurs through different types of alleles; at one extreme are mutations that cause Mendelian disease such as familial hypercholesterolemia arising from mutations in the LDL receptor with powerful phenotypic effects; at the other are common alleles (eg. ApoE) with small phenotypic effects. In the middle are 'Goldilocks alleles' (e.g., PCSK9) where the mutations are common enough to be useful in epidemiological analyses (in contrast to Mendelian) but still produce detectable biochemical effects. (Cohen, 2013)
- Fetal androgen production, especially testosterone, needs to be 'just right' to ensure the appropriate developmental trajectory of the fetus and offspring, while inappropriate fetal androgen or androgen signalling – both too little and too much - is associated with disorders of male reproductive development as well as being implicated in Polycystic Ovarian Syndrome in women (Fowler and O'Shaughnessy 2013).

#### *Human Behaviour Goldilocks zones*

- Social auditory stimuli intermediate between 'predictable' and 'complex' best serve the selective attention of 7-8-month old infants: Kidd et al (2016)
- An optimal amount of social interactivity of television watching promotes children's visual attention and word learning (Nussenbaum and Amso, 2016).
- When considering the wellbeing of adolescents, 'too little' digital screen use may deprive them of important social information and peer pursuits whereas 'too much' may displace other meaningful activities (Przybylski and Weinstein 2017)

#### *Human educational training needs Goldilocks zones*

- The degree of specialisation required to ensure the acquisition of professional competences in Paediatric Psychological training (Steele et al 2014)

#### *Healthcare*

- The 'Goldilocks point' in Palliative Care refers to exactly the right time to mobilise specialist hospital/palliative care services for the patient sub-group who will derive the most benefit. (LeBlanc et al 2014)
- The Goldilocks Principle is invoked in the regulation of healthcare to make sure it is not too little, nor too much but 'just right': Kemple (2016)

- The need for Children's Health Insurance to provide 'just the right health outcomes, just the right patient care experience and just the right costs': Szilagyi (2015)

Zeng H. (2017) mTOR signalling in immune cells and its implications for cancer immunotherapy. *Cancer Letters*; 408: 182-189

Walther V, Graham TA (2014) Location, location, location! The reality of life for an intestinal stem cell in the crypt. *J Pathol*; 234: 1-4.

Chiu H-C, Levy R, Borenstein E (2014). Emergent biosynthetic capacity in simple microbial communities. *PLOS Computational Biology*; 10: e1003695

Ringel-Scala VM, McDaniel DK, Allen IC (2016) The Goldilocks Conundrum: NLR inflammasome modulation of gastrointestinal inflammation during inflammatory bowel disease. *Crit Rev Immunol*; 36: 283-314

Braune EB, Lendahl U (2016) Notch- a goldilocks signalling pathway in disease and cancer therapy. *Discov Med*; 115: 189-196

Nicholls SM, Clare A and Randall JC (2013) Goldilocks: a tool for identifying regions that are 'just right'. *Bioinformatics*; 32: 2047-2049

Schiffhauer ES, Luo T, Mohan K, Srivastava V, Qian X, Griffis, ER Iglesias PA, Robinson DN (2016) Mechanoaccumulative elements of the mammalian actin cytoskeleton. *Curr Biol*; 26: 1473-1479.

Domingo-Gonzalez R, Prince O, Cooper A, Khader SA (2016) Cytokines and chemokines in *Mycobacterium tuberculosis* infection. *Microbiol Spectr*; 4 doi 10.1128/microbiol-spec. TBTB2-oo18-2016.

Houlihan G, Arangundy-Franklin S, Holliger P (2017). Exploring the chemistry of genetic information storage and propagation through polymerase engineering. *Acc Chem Res*; 50: 1079-1087

Aubot BE, Hailie KL, Fattet L, Jennings PA, Adams JA (2017) Redirecting SR protein nuclear trafficking through an allosteric platform. *J Mol Biol*; 429: 2178-2191

Boothby M, Williams GL (2012) The Goldilocks effect. *Sci Transl Med*; 4:163fs42

Laskowski AI Knoepfler PS (2012) Utf1:Goldilocks for ES Bivalency. *Cell Stem Cell* 7:732-734

Baughman RP, Lower EE (2014) Goldilocks, vitamin D and sarcoidosis. *Arthritis Res Ther* 16: 111-113

Seidelmann SB, Claggett B, Cheng S, Henglin M, Shah A, Steffen LM, Folsom AR, Rimm EB, Willett Wc, Solomon SD (2018) Dietary carbohydrate intake and mortality: a prospective cohort study and meta-analysis. *The Lancet* on line August 16 2018  
<http://cix.doi.org/10.1016/S2468-2667> (18)30135-X

Alleman RJ, Katunge LA, Nelson MAM, Brown DA, Anderson EJ (2014). The 'Goldilocks Zone' from a redox perspective – Adaptive vs. deleterious responses to oxidative stress in striated muscle. *Frontiers in Physiology*; 5: 1-20.

Leijten J, Chair YC, Papantoniou I, Gens L, Schrooten J, Luyten FP (2015). Cell-based advanced therapeutic medicinal products for bone repair: Keep it simple? *Advanced Drug Delivery Reviews* 84: 30-44

Koebele SV, Bimonte-Nelson HA (2015). Trajectories and phenotypes with estrogen exposures across the lifespan: What does Goldilocks have to do with it? *Horm Behav* 74: 86-104

Padayatty SJ, Levine M (2016). Vitamin C physiology: the known and the unknown Goldilocks. *Oral Dis* 22: 463-493

Ladabaum U, Schoen RE (2016) Post-polypectomy surveillance that would please Goldilocks – not too much, not too little, but just right. *Gastroenterology*; 150: 791-796.

Clancy KBH (2007) Inflammation, Reproduction, and the Goldilocks Principle. In KBH Clancy, K Hinde, K and JN Rutherford: *Building babies: primate development in proximate and ultimate perspective*. *Developments in Primatology* 37, DOI 10.1007/978-1-4614-4060\_1 Springer Science+Business Media New York, p4614-4060.

Cuthbertson BH (2013) Goldilocks, elephants and surgical fluids. *Br J Anaesth*; 110, 144–145, <https://doi.org/10.1093/bja/> ...

Jagsi R (2016) Goldilocks and margins for DCIS: identifying 'just right'. *Practical radiation oncology* 6: 296-297.

Humphries MD (2016) The Goldilocks zone in neural circuits. *eLife* 5: e22735

Kerr M, Dodd MS, Heather LC (2017) the 'Goldilocks zone' of fatty acid metabolism; to ensure that the relationship with cardiac function is just right. *Clin Sci* 131: 2079-2094.

Fatovich DM (2017). The time paradox of emergency medicine: another inverted U curve. *Emerg Med Australas* 29: 730-732.

Milner PI (2017) Keeping joints healthy: The Goldilocks effect of exercise. *Veterinary Journal* 226: 4-5.

Sweitzer BJ, Howell SJ (2017) The Goldilocks principle as it applies to perioperative blood pressure: what is too high, too low, or just right? *Br J Anaesth* 119: 7-10

Boothroyd A, Mackersie C (2017) A 'Goldilocks' approach to hearing-aid self-fitting: user interactions. *Am J Audiol*; 26: 430-435

Martin D, Grocott M (2017) Oxygen therapy and the Goldilocks principle. *J Intensive Care Soc* 18: 279-281

Broglio KR, Connor JT, Berry SM (2014) Not too big, not too small: a goldilocks approach to sample size selection 24: 685-705

Tansy AP, Liebeskind DS (2013). The goldilocks dilemma in acute ischemic stroke. *Front Neurol* 4: 164-166.

Frenz DA, Liu W, Cveki A, Xie Q, Wassef L, Loredana Q, Niederreither K, Maconochie, M Shanske A (2010) Retinoid signalling in inner ear development: a 'Goldilocks' phenomenon. *Am J Med Genet A* 152A: 2947-2961

Grossman SA, Kleinberg L (2017) A search for the 'Goldilocks zone' with regard to the optimal duration of adjuvant temozolomide in patients with glioblastoma. *Neuro-Oncology* 19: 1019-1020

Dean CH, Lloyd CM (2017) Lung alveolar repair: not all cells are equal. *Trends Mol Med* 23: 871-873.

Magnowski A, Brown M, Schramm K, Lindquist J, Rochun PJ, Johnson T (2017). The law of unintended consequences: current design challenges in inferior vena cava filters; *Expert Rev Med Devices* 14: 805-810

Cohen JC (2013) Emerging LDL therapies: using human genetics to discover new therapeutic targets for plasmas lipids. *J Clin Lipidol* 7: S1-S5

Fowler PA, O'Shaughnessy PJ (2013). The Goldilocks principle and developmental androgens in males; what is "just right"? *Endocrinology* 154: 1663-1671.

Kidd C, Piantadosi ST, Aslin RN (2014) The Goldilocks effect in infant auditory attention. *Child Dev* 85: 1795-1804

Nussenbaum K, Amso D (2016) An attentional Goldilocks effect: an optimal amount of social interactivity promotes word learning from video. *J Cogn Dev* 17: 30-40.

Przybylski A, Weinstein N (2017) A large-scale test of the Goldilocks hypothesis: quantifying the relations between digital-screen use and the mental well-being of adolescents. *Psychol Sci* 28: 204-215

Steele RG, Borner KB, Roberts MC (2014) Commentary: finding the middle bowl: Goldilocks' lessons on professional competences in pediatric psychology' *J Pediat Psychol* 39: 988-997

LeBlanc TW, Currow DC, Abernethy AP (2014) On Goldilocks, care coordination, and palliative care: making it 'just right'. *Prim Care Respir J* 23: 8-10

Kemple T (2016) The Goldilocks problems in regulation. *BMJ* 2016; 354:i3778

Szilagyi PG (2015) The children's'. health insurance program and the Goldilocks effect. *Acad Pediatr* 15: S13-S14