References 9

Links, Abstracts, Articles, etc.

These links should work as of 2014; sometimes you have to click on them several times; if they don't work, then Google/search the titles

http://www.nature.com/nbt/journal/v18/n10s/full/nbt1000_IT7.html Autoimmune disease Rapid progress in our understanding of immune function promises more effective treatments for autoimmune disorders. "*The hypothesis is that these pathogens might trigger an autoimmune response by virtue of these homologies. For example, the novel thyroid autoantigen that is the sodium/iodide symporter (NIS) has local amino acid sequence homologies with three other known thyroid autoantigens, namely thyroglobulin, thyroid peroxidase, and thyrotropin receptor. A recent report describes the application of a computer-aided search that shows NIS to have significant local homologies with no fewer than 11 other proteins from bacteria or viruses, such as Streptococcus or herpes. NIS was also found to have extensive—but not local—homologies with several unknown proteins from invertebrates such as Drosophila melanogaster and Caenorhabditis elegans, and with bacteria such as Bacillus subtilis and Xanthobacter.*"

http://eje-online.org/content/165/2/177.long Phosphodiesterases in endocrine physiology and disease. *"The cAMP–protein kinase A pathway plays a central role in the development and physiology of endocrine tissues. cAMP mediates the intracellular effects of numerous peptide hormones. Various cellular and molecular alterations of the cAMP-signaling pathway have been observed in endocrine diseases. Phosphodiesterases (PDEs) are key regulatory enzymes of intracellular cAMP levels. Indeed, PDEs are the only known mechanism for inactivation of cAMP by catalysis to 50-AMP. It has been suggested that disruption of PDEs could also have a role in the pathogenesis of many endocrine diseases. This review summarizes the most recent advances concerning the role of the PDEs in the physiopathology."* (My note: see "The Tyrosine Connection" references for TDP2 PDE's also).

http://www.jbc.org/content/250/7/2452.long Cyclic Nucleotide Phosphodiesterases and Thyroid Hormones

http://www.ncbi.nlm.nih.gov/pubmed/6162987 EFFECT OF THYROID HORMONE ON CYCLIC AMP PHOSPHODIESTERASE IN RAT KIDNEY

http://journals.lww.com/jto/Fulltext/2010/10001/Imaging_Thymoma.9.aspx Imaging Thymoma

https://www.jstage.jst.go.jp/article/antibiotics1968/46/7/46_7_1145/_article EFFECT OF CEPHALOSPORINS ON y-AMINOBUTYRIC ACID RECEPTOR BINDING WITH OR WITHOUT NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

http://www.biomedcentral.com/1741-7015/11/96 Phosphodiesterase 4-targeted treatments for autoimmune diseases

http://www.nature.com/horizon/rna/background/interference.html RNA INTERFERENCE: THE NEXT GENETICS REVOLUTION?

http://www.ncbi.nlm.nih.gov/pubmed/21624498 Pharmaceutical drug transport: The issues and the implications that it is essentially carrier-mediated only. *"All cells necessarily contain tens, if not hundreds, of carriers for nutrients and intermediary metabolites, and the human genome codes for more than 1000 carriers of various kinds. Here, we illustrate using a typical literature example the widespread but erroneous nature of the assumption that the 'background' or 'passive' permeability to drugs occurs in the absence of carriers. Comparison of the rate of drug transport in natural versus artificial membranes shows discrepancies in absolute magnitudes of 100-fold or more, with the carrier-containing cells showing the greater permeability*."

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2375356/ How to calculate the dose of chemotherapy. "*Typically there is a 4 – 10-fold variation in cytotoxic drug clearance between individuals due to differing activity of drug elimination processes related to genetic and environmental factors (Gurney, 1996). For example, the activity of cytochrome P450 (CYP) 3A4/5, the major oxidising enzymes for many cytotoxic drugs varies by as much as 50-fold (Wrighton et al, 1996). A common single-nucleotide polymorphism (SNP) or CYP3A5 has recently been identified and others are being searched for (Kuehl et al, 2001). In addition many drugs and disease states are known to inhibit or induce CYP activity further adding to this variation (George et al, 1996). Another example is the eight-fold variation in dihydropyrimidine dehydrogenase (DPD) activity, the enzyme that catabolises 5FU (Etienne et al, 1994) . . . A number of SNPs have also recently been identified for the steroid and xenbiotic receptor (SXR), a common-pathway receptor which transcriptionally activates a number of the drug elimination genes such as CYP3A4, MRP2 and MDR1 (Zhang et al, 2001).* (My note: an excellent paper to read about how to dose chemotherapy agents – and FQ's are chemo agents.)

http://www.aafp.org/afp/2007/0801/p391.html The Effect of Cytochrome P450 Metabolism on Drug Response, Interactions, and Adverse Effects. *"A specific gene encodes each CYP450 enzyme. Every person inherits one genetic allele from each parent. Alleles are referred to as "wild type" or "variant," with wild type occurring most commonly in the general population. An "extensive" (i.e., normal) metabolizer has received two copies of wild-type alleles. Polymorphism occurs when a variant allele replaces one or both wild-type alleles. Variant alleles usually encode a CYP450 enzyme that has reduced or no activity.1 Persons with two copies of variant alleles are "poor" metabolizers, whereas those with one wild-type and one variant allele have reduced enzyme activity. Finally, some persons inherit multiple copies of wild-type alleles, which results in excess enzyme activity. This phenotype is termed an "ultrarapid" metabolizer . . . CYP450 enzyme polymorphism is responsible for observed variations in drug response among patients of differing ethnic origins.4–6 For example, 7 percent of white persons and 2 to 7 percent of black persons are poor metabolizers of drugs dependent on CYP2D6, which metabolizes many beta blockers, antidepressants, and opioids.7,8 One in five Asian persons is a poor metabolizer of drugs dependent on CYP2C19, which metabolizes phenytoin (Dilantin), phenobarbital, omeprazole*

(Prilosec), and other drugs.9 Variance in drug response among persons of different ethnic origins also can be caused by genetic variations in other drug-metabolizing enzymes, drug transporters, and drug receptors."

http://www.pnas.org/content/105/37/13829.full.pdf Enzymes with lid-gated active sites must operate by an induced fit mechanism instead of conformational selection

http://eprints.bbk.ac.uk/986/ Methods to Characterize the Structure of Enzyme Binding Sites (Kahraman, A. and Thornton, Janet M. (2008) Methods to characterize the structure of enzyme binding sites. In: Schwede, T. and Peitsch, M.C. (eds.) Computational Structural Biology: Methods & Applications Vol. 1. Singapore: World Scientific Pub. Co., pp. 189-221. ISBN 9789812778789) (My note: I was able to download for free).

http://genome.cshlp.org/content/22/9/1599.full Decoding the human genome

http://www.greyhoundadoptionofoh.org/Greyhound_Health_Packet_08.pdf Greyhound Medical Idiosyncrasies

http://pamw.pl/sites/default/files/PAMW%206%202009_Gluck_0.pdf Coexistence of two types of allergic hypersensitivity to drugs (FQ and Iodine sensitivity).

http://www.ncbi.nlm.nih.gov/pubmed/3037606 Circadian rhythms in mammalian neurotransmitter receptors

http://www.ncbi.nlm.nih.gov/pubmed/19708721 Neurobiology of circadian systems

https://www.utoledo.edu/med/depts/physpharm/ceder/pdfs/Tamara_-_Circadian_rhythms_of_.pdf Circadian rhythms of dopamine, glutamate and GABA in the striatum and nucleus accumbens of the awake rat: modulation by light

http://www.unifr.ch/biochem/assets/files/albrecht/publications/AlbrechtSleep2012.pdf Circadian rhythms and sleep—the metabolic connection

http://www.ncbi.nlm.nih.gov/pubmed/1784430 Circadian rhythm of cortical acetylcholine release as measured by in vivo microdialysis in freely moving rats.

http://www.ncbi.nlm.nih.gov/pubmed/21115064 The cholinergic system, circadian rhythmicity, and time memory.

http://www.ncbi.nlm.nih.gov/pubmed/9573384 Diurnal rhythms in ornithine decarboxylase activity and norepinephrine and acetylcholine synthesis in submaxillary lymph nodes and spleen of young and aged rats during Freund's adjuvant-induced arthritis.

https://www.utoledo.edu/med/depts/physpharm/ceder/pdfs/Tamara_-_Circadian_rhythms_of_.pdf Circadian rhythms of dopamine, glutamate and GABA in the striatum and nucleus accumbens of the awake rat: modulation by light

http://www.researchgate.net/publication/13429913_Diurnal_rhythms_in_norepinephrine_and_acetylcholine_synthesis_of_sympathetic_ganglia_heart_and_adrenals_of_aging_rats_effect_of_melatonin Diurnal rhythms in norepinephrine and acetylcholine synthesis of sympathetic ganglia, heart and adrenals of aging rats: effect of melatonin.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2988997/ Towards a unifying, systems biology understanding of large-scale cellular death and destruction caused by poorly liganded iron: Parkinson's, Huntington's, Alzheimer's, prions, bactericides, chemical toxicology and others as examples. "*Exposure to a variety of toxins and/or infectious agents leads to disease, degeneration and death, often characterised by circumstances in which cells or tissues do not merely die and cease to function but may be more or less entirely obliterated. It is then legitimate to ask the question as to whether, despite the many kinds of agent involved, there may be at least some unifying mechanisms of such cell death and destruction. I summarise the evidence that in a great many cases, one underlying mechanism, providing major stresses of this type, entails continuing and autocatalytic production (based on positive feedback mechanisms) of hydroxyl radicals via Fenton chemistry involving poorly liganded iron, leading to cell death via apoptosis (probably including via pathways induced by changes in the NF-κB system). While every pathway is in some sense connected to every other one, I highlight the literature evidence suggesting that the degenerative effects of many diseases and toxicological insults converge on iron dysregulation. This highlights specifically the role of iron metabolism, and the detailed speciation of iron, in chemical and other toxicology, and has significant implications for the use of iron chelating substances (probably in partnership with appropriate anti-oxidants) as nutritional or therapeutic agents in inhibiting both the progression of these mainly degenerative diseases and the sequelae of both chronic and acute toxin exposure*."

http://www.ncbi.nlm.nih.gov/pubmed/14641268 The influence of ageing on the insulin signalling system in rat lacrimal and salivary glands

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3340573/ Prevention of anaphylaxis related to mast cell activation syndrome with omalizumab

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1693097/ On the origin of mitochondria: a genomics perspective

http://www.nature.com/srep/2014/140127/srep03887/full/srep03887.html Simultaneous quantification of mitochondrial DNA copy number and deletion ratio: A multiplex real-time PCR assay

http://www.ncbi.nlm.nih.gov/pubmed/16297466 Pregnane and Xenobiotic Receptor (PXR/SXR) resides predominantly in the nuclear compartment of the interphase cell and associates with the condensed chromosomes during mitosis

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC317112/ Reciprocal activation of Xenobiotic response genes by nuclear receptors SXR/PXR and CAR. "*The liver cytochrome P450 (CYP) enzymes represent a supergene family of hemeproteins that catalyze the metabolic conversion to more polar derivatives of an amazing diversity of foreign chemicals (xenobiotics) including various environmental pollutants,*

carcinogens, and prescription drugs as well as endogenous substrates such as steroid hormones. The levels of some CYP enzymes are typically induced by their xenobiotic substrates. For example, administration of glucocorticoids (both agonists such as dexamethasone [DEX] and antagonists such as RU486), rifampicin (RIF), or Phenobarbital (PB) increases the levels of CYP3A, a family of medically significant isoenzymes involved in the metabolism of more than half of all prescription drugs as well as neutraceuticals and herbal medicines."

http://www.ismp.org/quarterwatch/pdfs/2011Q4.pdf Quarter Watch, Monitoring FDA MedWatch Reports, New Data from 2011, Quarters 3-4. Based on number direct reports to FDA in 2011, Levaquin is FDA's 3rd most dangerous drug.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2755150/ Ciprofloxacin Induced Nightmares in an Adult Patient

http://www.ncbi.nlm.nih.gov/pubmed/21882233 Conventional Apheresis Therapies: A Review. (My note: I wish this would be considered during the acute phase of floxing – or any time after if symptomatic -- if these are Ab/Ig mediated rxns, this might help? – read full paper).

http://www.departmentofmedicine.com/rounds/presentations/2012/hemo/plasmapheresis_review_ttp.pdf A General Overview of Plasmapheresis and a Review of TTP

http://www.ncbi.nlm.nih.gov/pubmed/22365088 Nonclassical Biological Activities of Quinolone Derivatives

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3102705/ Lymphoadenopathy during Lyme Borreliosis Is Caused by Spirochete Migration-Induced Specific B Cell Activation

No link: need to Google. Running title: Platelet 5-HT and MAO B in hypothyroidism. Authors: Stipcevic Tamara Kusacic-Kuna Sanjab Dezeljin Martina Dodig Damir Korsic Mirko Pivac Nela Muck-Seler Dorotea

http://www.ncbi.nlm.nih.gov/pubmed/18294189 Chronic tendinopathy tissue pathology, pain mechanisms, and etiology with a special focus on inflammation

http://www.ncbi.nlm.nih.gov/pubmed/24027089 The Pain of Tendinopathy: Physiological or Pathophysiological? *"Tendon pain remains an enigma. Many clinical features are consistent with tissue disruption—the pain is localised, persistent and specifically associated with tendon loading, whereas others are not—investigations do not always match symptoms and painless tendons can be catastrophically degenerated. As such, the question 'what causes a tendon to be painful?' remains unanswered. Without a proper understanding of the mechanism behind tendon pain, it is no surprise that treatments are often ineffective."*

http://www.ncbi.nlm.nih.gov/pubmed/12499631 Neuroprotective Effects of the Green Tea Components Theanine and Catechins

http://www.jimmunol.org/content/179/1/665.long Fullerene Nanomaterials Inhibit the Allergic Response

http://www.sciencedirect.com/science/article/pii/S0142961212003237 The prolongation of the lifespan of rats by repeated oral administration of [60] fullerene

Need to google to get link: Corrigendum to "The prolongation of the lifespan of rats by repeated oral administration of [60]fullerene" [Biomaterials 33 (2012) 4936e4946]

http://www.ncbi.nlm.nih.gov/pubmed/17579089 Fullerene nanomaterials inhibit the allergic response.

http://www.ncbi.nlm.nih.gov/pubmed/17914184 Effects of dietary supplementation with N-acetyl cysteine, acetyl-L-carnitine and S-adenosyl methionine on cognitive performance and aggression in normal mice and mice expressing human ApoE4

http://www.ncbi.nlm.nih.gov/pubmed/18373034 Dietary and genetic compromise in folate availability reduces acetylcholine, cognitive performance and increases aggression: critical role of S-adenosyl methionine.

http://www.ncbi.nlm.nih.gov/pubmed/20399762 N-acetylcysteine prevents memory deficits, the decrease in acetylcholinesterase activity and oxidative stress in rats exposed to cadmium.

http://www.ncbi.nlm.nih.gov/pubmed/21761386 Anti-inflammatory efficacy of N-acetylcysteine and therapeutic usefulness.

http://smj.psmmc.med.sa/index.php/smj/article/viewFile/5918/3692 Does N-acetylcysteine have an effect on acetylcholine-induced contractions and histopathological changes on isolated rat ileum?

https://www.pinnaclife.com/sites/default/files/research/NAC_and_Learning_and_Memory.pdf Protective effect of N-acetyl-L-cysteine on amyloid β-peptide-induced learning and memory deficits in mice

http://www.lef.org/magazine/2010/5/N-Acetyl-Cysteine/Page-01?checked=1 The Overlooked Compound That Saves Lives

https://www.idtdna.com/pages/docs/educational-resources/mitochondrial-dna.pdf?sfvrsn=4 Integrated DNA Technologies: Mitochondrial DNA (mtDNA)

http://online.liebertpub.com/doi/abs/10.1089/rej.2004.7.171 Mitochondrial Mutations in Mammalian Aging: An Over-Hasty About-Turn?

http://www.biomedcentral.com/1471-2164/8/293 The mitochondrial DNA control region shows genetically correlated levels of heteroplasmy in leukocytes of centenarians and their offspring

http://cshperspectives.cshlp.org/content/5/11/a021220.full Mitochondrial DNA Genetics and the Heteroplasmy Conundrum in Evolution and Disease

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4191934/pdf/pgen.1004670.pdf Keeping mtDNA in Shape between Generations

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2593138/pdf/nihms75336.pdf Estrogenic Control of Mitochondrial Function and Biogenesis

https://www.bioscience.org/2007/v12/af/2128/fulltext.htm Pesticides and impairment of mitochondrial function in relation with the parkinsonian syndrome

http://www.ncbi.nlm.nih.gov/pubmed/10048748 Chromosomal aberrations in human lymphocytes exposed in vitro to enrofloxacin and ciprofloxacin.

http://journals.tubitak.gov.tr/medical/issues/sag-04-34-5/sag-34-5-4-0401-1.pdf Genotoxic Evaluation of the Antibacterial Drug, Ciprofloxacin, in Cultured Lymphocytes of Patients with Urinary Tract Infection

Glutamate Excess in Multiple Sclerosis Variants Glutamate Excess in Multiple Sclerosis Variants

http://www.lymeneteurope.org/forum/viewtopic.php?f=8&t=4474 Anti-NMDA receptor encephalitis

https://www.pharmgkb.org/pathway/PA166041114 Ibuprofen Pathway, Pharmacokinetics

http://en.wikipedia.org/wiki/Prostaglandin-endoperoxide_synthase_2 Prostaglandin-endoperoxide synthase 2

http://en.wikipedia.org/wiki/Organic_peroxide Organic peroxide

http://en.wikipedia.org/wiki/Quercetin Quercetin

http://en.wikipedia.org/wiki/Luteolin Luteolin

http://www.mastokids.org/degranular.html Mastokids: Supporting Families Living With Pediatric Mastocytosis

http://medicalxpress.com/news/2015-03-statins-diabetes-percent.html Study shows that use of statins increases risk of developing diabetes by 46 percent

http://www.newsweek.com/first-human-adaptation-toxic-chemical-uncovered-311288 First Human Adaptation to Toxic Chemical Uncovered

http://www.mpg.de/5567995/artificial_thymus_immune_cells Artificial thymus tissue enables maturation of immune cells

http://cdn.intechopen.com/pdfs-wm/37919.pdf Paracrine Regulation of Thyroid-HormoneSynthesis by C Cells. *"The DNES (Diffuse Neuroendocrine System) includes, besides C cells, gastroenteroendocrine cells, pancreatic islet cells, bronchopulmonary and urogenital endocrine cells, adenohypophyseal cells, parathyroid cells and chromaffin cells of the adrenal medulla, carotid body, and sympathetic ganglia . . . The C cells share with other neuroendocrine cells the expression of different characteristic*

*neuroendocrine markers, such as chromogranin, synaptophysin and NSE, with chromogranin A as the most reliable marker generally used to characterize cells of DNES (see Figure 4). Most of those neuroendocrine markers are shared with different populations of nervous cells (Table 1). In addition to calcitonin, C cells may also contain many other regulatory peptides (Table 2), such as calcitonin gene-related peptide (CGRP) [30], katacalcin [31] or GRP [32]. Somatostatin has also been identified within C cells of most species. In the adult rabbits, bats and guinea pigs, most calcitonin-positive cells also contain somatostatin; however, in adult human and rat thyroid glands, only a small proportion of the calcitonin-positive cells are also somatostatin positive [33]. Similarly, peptides including neuromedin U [34] and helodermin-like peptide [35], have been demonstrated to colocalize with CT in normal C cells. Lately, a new generation of regulatory peptides, similar to those characteristically found in some hypothalamic nuclei, such as TRH [36], CART [37] or ghrelin [38], has increased the long list of substances synthesized by C cells. In addition to the regulatory peptide products, C cells also contain a variety of biologically active amines including serotonin [41] and melatonin [45] (see Table 2). Additionally, C cells are also implicated in the synthesis of many other different substances, such as tetranectin [50] or CEA [51] (see Table 3). (*My note: C cells, or their receptors or numerous markers or products, may be yet another potential direct target of FQ's to consider, contributing to widespread symptomatology. Or, in the case of destructive thyroiditis, I would imagine C cell destruction would occur along with thyroid follicular destruction also.*)*

http://www.thyroidscience.com/reviews/lowe.yellin.6.17.08/ithr.review.6.17.08.pdf Inadequate Thyroid Hormone Regulation as the Main Mechanism of Fibromyalgia: A Review of the Evidence

http://www.currentpsychiatry.com/home/article/supercharge-antidepressants-by-adding-thyroid-hormones/bc40b4227c8139f80cd73a09ebc44582.html 'Supercharge' antidepressants by adding thyroid hormones

http://www.nature.com/mp/journal/v7/n2/full/4000963a.html Thyroid hormones, serotonin and mood: of synergy and significance in the adult brain. *"The use of thyroid hormones as an effective adjunct treatment for affective disorders has been studied over the past three decades and has been confirmed repeatedly. Interaction of the thyroid and monoamine neurotransmitter systems has been suggested as a potential underlying mechanism of action. While catecholamine and thyroid interrelationships have been reviewed in detail, the serotonin system has been relatively neglected. Thus, the goal of this article is to review the literature on the relationships between thyroid hormones and the brain serotonin (5-HT) system . . . Disorders of the thyroid gland are frequently associated with severe mental disturbances.1,2 This intimate association between the thyroid system and behavior has been the impetus for exploring the effects of thyroid hormones in modulating affective illness, and the role of the hypothalamic-pituitary thyroid (HPT) axis in the pathophysiology of mood disorders.3 Thyroid hormones (TH) have a profound influence on behavior and mood, and appear to be capable of modulating the phenotypic expression of major affective illness.3,4,5,6 Thyroid supplementation is now widely accepted as an effective treatment option for patients with affective disorders.7,8,9"*

http://news.yahoo.com/10-169-blood-test-everything-170003116.html A $10,169 blood test is everything wrong with American health care. *"And that all makes it a bit baffling why, in California, a*

lipid panel can cost anywhere between $10 and $10,000. In either case, it is the exact same test. "We're not talking twofold or threefold variation. It's a different level of magnitude . . . "There's no other industry where you see this kind of extreme variation," Hsia says. "And nobody has ever really challenged it. It shows an extreme inefficiency, and something we really need to change."

http://en.wikipedia.org/wiki/Thymosins Thymosins

http://en.wikipedia.org/wiki/Ubiquitin Ubiquitin

http://www.genome.gov/26524162 Bringing the Genomic Revolution to the Public

http://www.sciencemag.org/site/products/fungen.xhtml Functional Genomics Revolution

http://www.newsmax.com/Health/Health-News/blood-test-antiobiotic/2015/03/19/id/631241/ Rapid Blood Test Promises to Cut Antibiotic Overuse

http://www.microbecolhealthdis.net/index.php/mehd/article/view/26382 An n=1 case report of a child with autism improving on antibiotics and a father's quest to understand what it may mean

http://www.thedailybeast.com/articles/2014/04/14/how-being-a-doctor-became-the-most-miserable-profession.html How Being a Doctor Became the Most Miserable Profession Nine of 10 doctors discourage others from joining the profession, and 300 physicians commit suicide every year. When did it get this bad? (My note: reading the comments are enlightening).

http://en.wikipedia.org/wiki/Dock8 Dock8

http://en.wikipedia.org/wiki/Transamination Transamination

http://www.ncbi.nlm.nih.gov/pubmed/16078324 Clinical and serological heterogeneity in patients with anticentromere antibodies.

http://www.ncbi.nlm.nih.gov/pubmed/12605324 Antitopoisomerase I antibody in patients with systemic lupus erythematosus/sicca syndrome without a concomitant scleroderma: two case reports.

http://www.ncbi.nlm.nih.gov/pubmed/9158085 Fine specificity of autoantibodies to La/SSB: epitope mapping, and characterization.

http://www.ncbi.nlm.nih.gov/pubmed/9115577 A frame shift mutation in a hot spot region of the nuclear autoantigen La (SS-B).

http://www.ncbi.nlm.nih.gov/pubmed/24296409 Interaction of cholinesterase modulators with DNA and their cytotoxic activity.

http://www.ncbi.nlm.nih.gov/pubmed/2456507 Antinuclear antibodies: diagnostic markers and clues to the basis of systemic autoimmunity.

http://www.ncbi.nlm.nih.gov/pubmed/19584730 Emerging new pathways of pathogenesis and targets for treatment in systemic lupus erythematosus and Sjogren's syndrome.

http://www.nature.com/nbt/journal/v18/n10s/full/nbt1000_IT7.html Autoimmune disease. Rapid progress in our understanding of immune function promises more effective treatments for autoimmune disorders.

http://www.ncbi.nlm.nih.gov/pubmed/19883799 Travels and travails of autoimmunity: a historical journey from discovery to rediscovery.

http://www.aarda.org/autoimmune-information/autoimmune-disease-in-women/ Autoimmune Disease in Women

http://www.diabetesed.net/page/_files/autoimmune-diseases.pdf The Cost Burden of Autoimmune Disease: The Latest Front in the War on Healthcare Spending

https://experiencelife.com/article/autoimmune-disorders-when-your-body-turns-on-you/ Autoimmune Disorders: When Your Body Turns On You

http://www.newswise.com/articles/profound-debiliating-fatigue-found-to-be-a-major-issue-for-autoimmune-disease-patients-in-new-national-survey Profound, Debilitating Fatigue Found to Be a Major Issue for Autoimmune Disease Patients in New National Survey. AARDA Calls on "Fuzzy," Largely Ignored Symptom to Become a New Focus of Research

http://ajp.psychiatryonline.org/doi/abs/10.1176/appi.ajp.2013.13010086 A Nationwide Study on the Risk of Autoimmune Diseases in Individuals With a Personal or a Family History of Schizophrenia and Related Psychosis

http://arbl.cvmbs.colostate.edu/hbooks/pathphys/endocrine/thyroid/nai_symport.html The Sodium-Iodide Symporter

http://medicine.ucsf.edu/education/resed/Chiefs_cover_sheets/thyroid_antibodies.pdf Thyroid Antibodies

http://www.ncbi.nlm.nih.gov/pubmed/22605538 Incidence of amiodarone hypersensitivity in patients with previous allergy to iodine or iodinated contrast agents.

http://www.ncbi.nlm.nih.gov/pubmed/15661464 ["Iodine allergy": point of view].

http://www.ncbi.nlm.nih.gov/pubmed/23743515 Nonimmediate hypersensitivity reactions to iodinated contrast media.

http://www.ncbi.nlm.nih.gov/pubmed/21656488 Pharmacotherapy of hyperthyreosis--adverse drug reactions.

http://www.ncbi.nlm.nih.gov/pubmed/21494128 Anesthesia in the patient with multiple drug allergies: are all allergies the same?

http://www.ncbi.nlm.nih.gov/pubmed/21123444 A new small-molecule antagonist inhibits Graves' disease antibody activation of the TSH receptor.

http://www.ncbi.nlm.nih.gov/pubmed/20025583 Effects of secondhand smoke on thyroid function.

http://academicdepartments.musc.edu/catalyst/archives/2015/4-3RxWatchdog.html Rx warning: possible mitochondrial toxicity. Charles Bennet MD, PhD/SONAR and Raja Fayad MD research.

http://www.ncbi.nlm.nih.gov/pubmed/25586498 Activity of quinolone CP-115,955 against bacterial and human type II topoisomerases is mediated by different interactions. *"CP-115,955 is a quinolone with a 4-hydroxyphenyl at C7 that displays high activity against both bacterial and human type II topoisomerases . . . Thus, quinolones may be a viable platform for the development of novel drugs with anticancer potential."*

http://www.ncbi.nlm.nih.gov/pubmed/24495080 Topoisomerase II and leukemia.

http://www.ncbi.nlm.nih.gov/pubmed/18922022 The efficacy of topoisomerase II-targeted anticancer agents reflects the persistence of drug-induced cleavage complexes in cells. *"Genistein, a widely consumed bioflavonoid with chemopreventative properties in adults, and etoposide, a commonly prescribed anticancer drug, are well-characterized topoisomerase II poisons. Although both compounds display similar potencies against human topoisomerase IIalpha and IIbeta in vitro and induce comparable levels of DNA cleavage complexes in cultured human cells, their cytotoxic and genotoxic effects differ significantly. As determined by assays that monitored cell viability or the phosphorylation of histone H2AX, etoposide was much more toxic in CEM cells than genistein. Further studies that characterized the simultaneous treatment of cells with genistein and etoposide indicate that the differential actions of the two compounds are not related to the effects of genistein on cellular processes outside of its activity against topoisomerase II. Rather, they appear to result from a longer persistence of cleavage complexes induced by etoposide as compared to genistein."*

http://www.ncbi.nlm.nih.gov/pubmed/10778981 Differential cytotoxic pathways of topoisomerase I and II anticancer agents after overexpression of the E2F-1/DP-1 transcription factor complex.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2679583/ DNA Topoisomerase II, Genotoxicity, and Cancer. *"Topoisomerases maintain genomic integrity during this process by forming covalent attachments between active site tyrosyl residues and the terminal DNA phosphates that are generated during the cleavage reaction [5,12,14–20]. This covalent linkage is the hallmark characteristic of all DNA topoisomerases . . . The central domain (amino acids ~671–1200) of topoisomerase II is homologous to the A subunit of DNA gyrase (GyrA) [14,19,48]. This portion of the enzyme contains the active site tyrosine (amino acid 805 for topoisomerase IIα and 821 for topoisomerase IIβ) required for DNA cleavage and ligation . . . Bioflavonoids, such as genistein, are polyphenolic compounds that are constituents of many fruits, vegetables, legumes, and plant leaves [105–107]. They are an integral component of the human diet and are believed to provide a number of health benefits to adults, including chemoprevention leaves [105–112]. Bioflavonoids have a variety of effects on human cells. They represent the most abundant natural source of antioxidants, potently inhibit tyrosine kinases, and exhibit*

anti-proliferative and pro-apoptotic affects leaves [105–109,112–116]. However, they also display cytotoxic and genotoxic properties and many are potent topoisomerase II poisons [117–120]. Although the physiological actions of bioflavonoids are complex, the sensitivity of cells to genistein-induced toxicity has been correlated to the activity of the type II enzyme [119,121]. Quinolones, such as CP-115,953, are the only drugs that show high activity against eukaryotic and prokaryotic type II enzymes [101,122–125]. While this last drug class has not yet been exploited to treat cancer, quinolones such as ciprofloxacin and levofloxacin that target bacterial type II topoisomerases are the most active and broad-spectrum oral antibacterials in clinical use [124,126,127] . . . Non-covalent topoisomerase II poisons vary dramatically in their DNA binding properties. For example, etoposide is a non-intercalative compound that displays weak, if any, interaction with DNA in the absence of topoisomerase II [81,128]. Similarly, genistein and quinolones are also non-intercalative [101,123–125,129] . . . It was originally thought that topoisomerase II-targeted drugs acted through interactions with DNA, "highjacking" the enzyme to sites of drug binding. We now believe that this is incorrect. All available evidence indicates that non-covalent topoisomerase II poisons act within the active site of the enzyme at the interface between the protein and DNA substrate [15,16,133–137]. Furthermore, mechanistic studies suggest that it is actually the interactions between topoisomerase II and these compounds that serve as the point of entry into the enzyme-DNA complex [135–138] . . . DNA breakpoints found in these secondary leukemias are in close proximity to topoisomerase II cleavage sites [144–146]. It is notable that therapy-related leukemias with 11q23 rearrangements are unique to chemotherapeutic regimens that contain topoisomerase II-targeted drugs [84,86,94,139] . . . A high percentage of infant leukemias also display translocations involving chromosomal band 11q23 [147]. Even though genistein and other bioflavonoids appear to be chemopreventative in adults, the maternal consumption (during pregnancy) of foods that are naturally high in these topoisomerase II poisons increases the risk of developing these infant leukemias more than 3- fold [148]. Once again, chromosomal breakpoints in these leukemias are proximal to topoisomerase II cleavage sites [149]."

http://www.ncbi.nlm.nih.gov/pubmed/25104093 The effects and underlying mechanism of excessive iodide on excessive fluoride-induced thyroid cytotoxicity. "*Collectively, excessive fluoride and excessive iodide have detrimental influences on human thyroid cells. Furthermore, an antagonistic interaction between fluoride and excessive iodide exists, and cytotoxicity may be related to IRE1 pathway-induced apoptosis*."

http://www.ncbi.nlm.nih.gov/pubmed/25164033 Ameliorative effect of resveratrol against fluoride-induced alteration of thyroid function in male wistar rats.

http://www.ncbi.nlm.nih.gov/pubmed/25141541 Effects of magnesium on cytomorphology and enzyme activities in thyroid of rats.

http://www.ncbi.nlm.nih.gov/pubmed/22365088 Nonclassical biological activities of quinolone derivatives.

http://en.wikipedia.org/wiki/Vosaroxin Vosaroxin

http://www.ncbi.nlm.nih.gov/pubmed/21252718 Phase II multicenter trial of voreloxin as second-line therapy in chemotherapy-sensitive or refractory small cell lung cancer. "Voreloxin is an anticancer quinolone derivative that intercalates DNA and inhibits topoisomerase II, causing double-strand breaks in DNA, irreversible G2 arrest, and rapid onset of apoptosis."

http://www.ncbi.nlm.nih.gov/pubmed/20419121 Voreloxin is an anticancer quinolone derivative that intercalates DNA and poisons topoisomerase II.

http://www.sunesis.com/data-pdf/595/sunesis-voreloxin-200904-AACR-2.pdf Voreloxin as a Topoisomerase II Poison: Role of DNA Intercalation

http://www.drugdevelopment-technology.com/projects/voreloxin/ Voreloxin, Anti-Cancer Quinolone Derivative, United States of America

http://meco-project.eu/sites/meco-project.eu/files/Karimi_0.pdf Drug Side-Effects: What Do Patient Forums Reveal?

Googled sodium iodide symporter phospholipase C

From a google book on internet: "Activation of phospholipase C regulates iodide reflux, the production of free iodide radicals, and the iodination of thyroglobulin".

From Werner and Ingbar's The thyroid: A fundamental and clinical . . . . Has a really good diagram and description of PLC and NIS connection. "At higher concentrations of TSH, stimulation of Gq/11 and the phospholipase C dependent inositol phosphate Ca2+/diacylglycerol pathway activates H2O2 generation and iodination. . . . NIS function is dependent on the electrochemical gradient generated by the Na+K+-ATPase. At the basolateral membrane, this also requires the presence of a constitutively active potassium channel consisting of the KCNQ1 and the KCNE2 subunits promoting K+ efflux. Targeted disruption of the KCNE2 subunit results in hypothyroidism with secondary dwarfism, alopecia, goiter and cardiac abnormalities. . . . The carboxy terminal region of the thyroglobulin monomer, encompassing residues 2,192 to 2,716 shares remarkable homology with AChE. This structure has been interpreted to indicate the possibility of a convergent origin of the TG gene from different ancestral DNA sequences. The AChE region is essential for normal conformational maturation, dimerization, and secretion of thyroglobulin. (look up research papers, no solid confirmation of cross reacting Ab's).

Analysis of sequence and structure homologies between thyroglobulin and acetylcholinesterase: Possible functional and clinical significance

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Abstract

The homology between thyroglobulin and acetylcholinesterase (1) has been analyzed in detail. It contains 28.3% identical amino acids and extends over 544 residues, involving more than 90% of the acetylcholinesterase molecule and the C-terminal portion of thyroglobulin. The hydropathy profiles of the homologous regions have been determined and compared. Their striking resemblance suggests that both proteins adopt a similar three dimensional structure and militates for some common property. As thyroglobulin and acetylcholinesterase are known to interact with cell membranes, we suggest that the acetylcholinesterase-like domain of thyroglobulin is involved in the binding. These observations demonstrate that thyroglobulin has evolved from the condensation of a duplicated copy of the acetylcholinesterase gene with an archaic thyroglobulin gene encoding the major hormonogenic domain. The extensive homology in hydropathy profiles suggests that the two proteins may share antigenic determinants. If this were the case, it would provide a rationale for the demonstration of immunoreactive thyroglobulin in neurons (2) and the pathogenesis of Grave's ophtalmopathy

My note: does the AChE part have a CoLQ? Does it have an active part with aromatic residues?

Endogenous expression of the sodium iodide symporter mediates uptake of iodide in murine models of colorectal carcinoma.

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ABSTRACT The sodium iodide symporter (NIS) mediates iodide uptake into the thyroid. Because of this mechanism, differentiated thyroid cancer is susceptible for radioiodine therapy. Functional NIS expression in extrathyroidal tumors has been reported mainly in breast cancer. We screened colorectal

tumors for NIS expression and investigated the mechanisms regulating NIS activity. Cell lines were screened for iodide uptake in vitro and NIS expression was evaluated by real-time RT-PCR, immunocytochemistry and immunoblotting. Iodide and pertechnetate uptake were evaluated in allograft tumors by biodistribution studies and scintigraphy. Tumors of transgenic mouse models for colorectal cancer harboring mutations in the oncogenes KRAS, beta-catenin or the tumor-suppressor gene adenomatous-polyposis coli (APC) were screened for NIS expression by RT-PCR. In vitro, functional NIS activity was detected in murine CMT93 rectal carcinoma cells and NIS expression was verified on mRNA and protein level. Inhibition of tyrosine kinases increased iodide uptake. Inhibition of tyrosine phosphatases decreased iodide uptake. In vivo, functional NIS expression was preserved in CMT93 tumors and tumor uptake could be enhanced by treatment of mice with tyrosine kinase inhibitors. In transgenic murine models of colorectal cancer, 14% of endogenous tumors expressed elevated levels of NIS mRNA. We conclude that NIS is functionally expressed in a subset of murine colorectal tumors and its activity is regulated by tyrosine phosphorylation. Therefore, with specific tyrosine kinase inhibition, these tumors might be susceptible for radioiodine treatment. Further studies are justified to identify the specific pathways regulating NIS activity and to transfer these findings to human cell lines and tissues.

Apremilast, Otezla, PDE-4

Thursday, November 13th, 2014

My husband suffered from a mild adverse reaction to fluoroquinolone antibiotics three years ago. He went on to develop psoriatic arthritis from his floxing approximately one year later. Psoriatic arthritis is a painful skin and joint inflammatory condition. He avoided taking any medications for this condition until just recently.

This past week he saw our rheumatologist who prescribed a brand new drug that has just come out on the market to treat psoriatic arthritis. The drug is called Otezla. The doctor told him that this medication was different than all of the other medications used to treat psoriatic arthritis because it does not suppress the immune system. He told him that the only known side effects that were seen in trials were diarrhea (which is supposed to get better the longer you use it), headaches, indigestion, nausea, vomiting, stomach pain, sinus problems and severe depression. The depression is so severe though and include suicidal ideation.

The doctor suggested that the Otezla, for the most part seemed harmless, and its side effects seemed nothing compared to all the other toxic drugs out there to treat this condition. So, my husband said he would give it a try and started the drug, three days ago.

Individuals prescribed this drug begin at a lower dose, 10 mg and titrate up to near a 100mgs within about month. Currently, because Otezla is so new, patients can only get the drug from their doctors. Physicians are being given one month trials of the medications from the pharmaceutical company to offer to their patients. If it works, the patient then orders directly from the manufacturer. Pharmacies are not distributing it yet.

My husband looked at the drug literature that came in the packet but it really did not give much information since it is just now being distributed out to the general market. The only thing that the literature can report is what was seen in the study trials and for the most part it just confirmed what the doctor had told us in clinic. The technical information was listed. The mechanisms of how the drug worked, how it is excreted and metabolized was in there but my husband did not understand much of it. Like a fool, I did not take the time to read it because I am dealing with my own health issues now.

The first day my husband used the Otezla, he had no problems, no side effects. We thought great, this is going to work without all the risks of the other drugs.

The second day he had to take two pills, one in the morning and one at night and again. Again, he did just fine.

The third day he woke up feeling very tired and began aching more than normal. Nevertheless, he decided to continue taking the drug. He took one pill in the morning and by that night he was really hurting all over; to the point that he was having a hard time walking and moving. Like a fool, he said he wanted to give it one more day and so he took the next pill.

That next morning, the fourth day, he could barely get up and was having severe pain in most of his tendons. He did stop taking the drug, but it was already too late. By that evening he could no longer move his right wrist without severe pain; pain that brought him to his knees. He also noticed his blood pressure was steadily climbing and his heart rate was abnormally high even at rest. The diarrhea then began with the stomach pain and now all his muscles were painful to touch. He was in bad shape.

He got on the internet and began searching for patient reports of side effects for Otezla. Lo and behold, there are already sites focused on Otezla side effects, though they are difficult to find (here, here) with all the marketing hype around this drug. Page after page on the search shows nothing but positive PR and how wonderful this drug is. He found reports tendon tears, all over muscle pain and nerve pain along with a host of what sounds very similar to post fluoroquinolone reactions – floxing symptoms. He also found a study on this drug that talked about this drug being shown to cause Achilles tendon ruptures and tears as a possible problem that should be listed in the literature but has not yet been put in there*. So, I said get me the drug literature paper so I can read it!

OMG! This drug is almost identical to the fluoroquinolones. Its active ingredient is Apremilast, not neldaxic acid. Both drugs use similar pathways. It has warnings not to be mixed with steroids, NSAIDs, Rifaximan and Phenobarbitol. Great, my husband was taking NSAIDs along with Otezla.

The paper then goes on to explain that this drug does not suppress the immune system like the other ones on the market, though it suppresses an immune activator called PDE4 (phosphodiesterase). However, many of the documents I read state that they do not know exactly how or why it works in half of all people or even how use it to treat psoriatic arthritis; meaning they really do not know what this drug is truly doing at the cellular level to the people taking it. DAMN IT!!!!!

Worse yet, in many using Otezla, it may cross the blood brain barrier and causing depression, psychosis and even suicidal thoughts and tendencies (sound familiar, Levaquin!) This drug literature was very similar to the early warnings for fluoroquinolones.

This new chemical, which is the active ingredient in this drug known as Apremilast was based on the thalidomide molecule, but it supposed to work differently. They are marketing it for autoimmune disease and if it goes over well they will expand on it to try and come up with better treatments for other autoimmune diseases like RA, Lupus, Crohns, etc…

Needless to say, my husband has stopped the drug but is now floxed even further. He did go to the ER because his wrist was so bad. In the ER, they determined that he has a swollen and possibly torn ulnar nerve that is damaged

just before the wrist. His Achilles tendon is now flaring today as well and he has been put in braces for both wrists and ankles. He is in terrible pain and on Oxicodone for the pain because he has been told not to take any NSAIDs from here on out due to after effects of Otezla.

Our lives where shattered when my husband, my daughter and myself took Cipro for a stomach infection three years ago; a stomach infection that turned out to be nothing more than a virus. I was hit the hardest. My daughter had a moderate adverse reaction and my husband only mildly. My daughter and I have gone on to develop spondyloarapthy with Crohn's and many other fluoroquinolone related problems. My husband went on to develop psoriatic arthritis but, for the most part, he could function with little problem. Now three years later and another drug, similar to the fluoroquinolones, has once again hit our family and shattered what was left of it. My husband is now very bad and we do not know if or when he will recover. This is very scary. I wrote this story to warn other floxies, individuals suffering from post fluoroquinolone reactions, not to take this drug.