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Four biomedical innovations I have been pursuing: Metastasis, Alzheimers, Clinical Trials and Biofuels

Metastasis

My mentor pioneered metastatic inflammatory extravasation [J Biomec Eng 8/90 v112 p295+, Cell. 2010 Mar 19;140(6):883-99; Cell. 2006 Jan 27;124(2):263-6] A seminar on antitrypsin made me curious but I found it causes metastasis [Mol Cell Proteomics. 2012 Nov;11(11):1320-39] causing me to find articles suggesting trypsin may me antimetastatic [BMJ p240 27Jan 1906; Cancer Res. 2003 Oct 15;63(20):6575-8; Cancer Chemother Pharmacol. 2001 Jul;47 Suppl:S16-22] THe exception that may prove the rule is that pancreatic cancer seems to "hide" perhaps because trypsin is made in the pancreas.

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From: vjp2@BioStrategist.com
Newsgroups: sci.med:556777
Subject: Trypsin v metastasis?
Date: Tue, 2 Aug 2016 00:32:33 +0000 (UTC)
Message-ID: nnopn1$puh$1@reader2.panix.com

   My mentor pioneered metastatic inflammatory extravasation, so when I
attended a talk on antitrypsin a few months ago, I began a jstor gedanken
experiment which led me to wonder if trypsin can combat metastasis.  Just a
crazy thought: would it make sence to give any cancer survivors with a
serious (eg strep) cold trypsin, heparin, and retanoic acid along with any
(mycin antibiotic; followed by a full body xray a month later. There's
another hunch I got about a strep/mycin/NMDAR pathway just anecdotally based
on folks I've know who got a bad cold just before their cancer showe dup.
I don't have any lab or funding, so I'm just guessing here.
   Immunity, inflammation, and cancer.  Grivennikov SI, Greten FR, Karin M.
Cell. 2010 Mar 19;140(6):883-99.  Inflammatory responses play decisive roles
at different stages of tumor development, including initiation, promotion,
malignant conversion, invasion, and metastasis.
   Macrophage diversity enhances tumor progression and metastasis.  Qian BZ,
Pollard JW.  Cell. 2010 Apr 2;141(1):39-51.  There is persuasive clinical and
experimental evidence that macrophages promote cancer initiation and
malignant progression. During tumor initiation, they create an inflammatory
environment that is mutagenic and promotes growth. As tumors progress to
malignancy, macrophages stimulate angiogenesis, enhance tumor cell migration
and invasion, and suppress antitumor immunity. At metastatic sites,
macrophages prepare the target tissue for arrival of tumor cells, and then a
different subpopulation of macrophages promotes tumor cell extravasation,
survival, and subsequent growth. Specialized subpopulations of macrophages
may represent important new therapeutic targets.
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Condeelis J, Pollard JW. Macrophages: obligate partners for tumor cell migration, invasion, and metastasis. Cell. 2006 Jan 27;124(2):263-6. Macrophages within the tumor microenvironment facilitate angiogenesis and extracellular-matrix breakdown and remodeling and promote tumor cell motility. Recent studies reveal that direct communication between macrophages and tumor cells leads to invasion and egress of tumor cells into the blood vessels (intravasation).

Nitric oxide synthase II suppresses the growth and metastasis of human cancer regardless of its up-regulation of protumor factors. Le X, Wei D, Huang S, Lancaster JR Jr, Xie K. Proc Natl Acad Sci U S A. 2005 Jun 14;102(24):8758-63. Inducible nitric oxide (NO) synthase (NOS) II has been implicated in macrophage-mediated antitumor activity. However, use of the NOS II gene in cancer therapy is problematic because of the double-edged nature of NO action. Herein we show that adenoviral vectors mediated effective NOS II gene transfer into various human tumors. Production of NO significantly up-regulated multiple angiogenic molecules. However, the NO-producing tumor cells did not form tumors or metastases in ectopic or orthotopic xenograft nude mouse models. The dramatic loss of malignancy was due to NO-mediated apoptosis.

A tumor-suppressive role for trypsin in human cancer progression. Yamashita K, Mimori K, Inoue H, Mori M, Sidransky D. Cancer Res. 2003 Oct 15;63(20):6575-8. Our results support the notion that trypsin plays a tumor-suppressive role in human carcinoma.

Mixture of trypsin, chymotrypsin and papain reduces formation of metastases and extends survival time of C57Bl6 mice with syngeneic melanoma B16. Wald M, Olejr T, Sebkov V, Zadinov M, Boubelk M, Pouckov P. Cancer Chemother Pharmacol. 2001 Jul;47 Suppl:S16-22. Our data suggest that serine and cysteine proteinases suppress B16 melanoma, and restrict its metastatic dissemination in C57B16 mice.

Trypsin In Cancer Author(s): F. W. Lambelle British Medical Journal, Vol. 1, No. 2402 (Jan. 12, 1907), p. 113

Secretomic analysis identifies alpha-1 antitrypsin (A1AT) as a required protein in cancer cell migration, invasion, and pericellular fibronectin assembly for facilitating lung colonization of lung adenocarcinoma cells. Chang YH, Lee SH, Liao IC, Huang SH, Cheng HC, Liao PC. Mol Cell Proteomics. 2012 Nov;11(11):1320-39. Molecular and pathological confirmation demonstrated that altered expression of A1AT correlates with the metastatic potential of lung adenocarcinoma. The migration and invasion properties of CL1-5 cells were significantly diminished by reducing the expression and secretion of their A1AT proteins.

Angiogenesis inhibition and tumor regression caused by heparin or a heparin fragment in the presence of cortisone. Folkman J, Langer R, Linhardt RJ, Haudenschild C, Taylor S. Science. 1983 Aug 19;221(4612):719-25. Heparin or a heparin fragment administered with cortisone inhibited angiogenesis, caused regression of large tumor masses, and prevented metastases.

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Alzhheimers

I met Stutzman jsut as protom pump inhibitors and wafrarin, both involving calcium channels, were implicated in Alzheimers.

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From: vjp2@BioStrategist.com
Newsgroups: sci.med:556778 sci.med.diseases.osteoporosis:14103
Subject: Sun vs Alzheimers?
Date: Tue, 2 Aug 2016 00:59:39 +0000 (UTC)
Message-ID: nnor9r$gfi$1@reader2.panix.com

 I attended a seminar by Stutzmann suggesting dantrolene and rapamycin as
Alzheimer treatment. A speculative jstor gedanken experiment that perhaps
too much sunless indoors causes modern prion neurodegenerative and other
aging diseases?
   The pathogenesis of Alzheimers disease is it a lifelong "calciumopathy"?
Stutzmann GE.  Neuroscientist. 2007 Oct;13(5):546-59.  Recent studies in AD
models have identified marked dysregulations in calcium signaling and related
downstream pathways, which occur long before the diagnostic histopathological
or cognitive changes. Under normal conditions, intracellular calcium signals
are coupled to effectors that maintain a healthy physiological state.
Consequently, sustained up-regulation of calcium may have pathophysiological
consequences. Indeed, upon reviewing the current body of literature,
increased calcium levels are functionally linked to the major features and
risk factors of AD: ApoE4 expression, presenilin and APP mutations, beta
amyloid plaques, hyperphosphorylation of tau, apoptosis, and synaptic
dysfunction.
   Dantrolene, A Treatment for Alzheimer's Disease?  Li Liang, M.D.a,b and
Huafeng Wei, M.D., Ph.Da, Alzheimer Dis Assoc Disord. 2015 Jan-Mar; 29(1):
1-5.  Previous studies support that the disruption of endoplasmic reticulum
(ER) Ca2+ via overactivation of Ryanodine receptors (RYRs) plays an important
role in the pathogenesis of AD. Normalization of intracellular Ca2+
homeostasis could be an effective strategy for AD therapies.  Recent
preclinical studies consistently support the therapeutic effects of
dantrolene in various types of AD animal models.
   Calcium channelopathies and Alzheimer's disease: insight into therapeutic
success and failures.  Chakroborty S, Stutzmann GE.  Eur J Pharmacol. 2014
Sep 15;739:83-95 Multifaceted involvement of calcium signaling in the
pathophysiology of Alzheimer's disease (AD), and summarize the various
therapeutic options currently available to combat this disease.
   Genetic reduction of mammalian target of rapamycin ameliorates Alzheimer's
disease-like cognitive and pathological deficits by restoring hippocampal
gene expression signature.  Caccamo A, De Pinto V, Messina A, Branca C, Oddo
S.  J Neurosci. 2014 Jun 4;34(23):7988-98 Elevated mammalian target of
rapamycin (mTOR) signaling has been found in Alzheimer's disease (AD)
patients and is linked to diabetes and aging, two known risk factors for AD.
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Novel mechanisms of calcium handling by the osteoclast Zaidi M1, Moonga BS, Adebanjo OA. Proc Assoc Am Physicians. 1999 Jul-Aug;111(4):319-27. The change in cytosolic Ca2+ is transduced finally into inhibition of bone resorption. It has been shown that a type 2 ryanodine receptor isoform, expressed uniquely in the plasma membrane, functions as a Ca2+ influx channel and possibly as a Ca2+ sensor. Ryanodine receptors are ordinarily Ca2+ release channels that have a microsomal membrane location in a wide variety of eukaryotic cells, including the osteoclasts.

Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Holick MF. Am J Clin Nutr. 2004 Dec;80(6 Suppl):1678S-88S. Solar ultraviolet B photons are absorbed by 7-dehydrocholesterol in the skin, leading to its transformation to previtamin D3, which is rapidly converted to vitamin D3. Vitamin D deficiency not only causes rickets among children but also precipitates and exacerbates osteoporosis among adults and causes the painful bone disease osteomalacia. Vitamin D deficiency has been associated with increased risks of deadly cancers, cardiovascular disease, multiple sclerosis, rheumatoid arthritis, and type 1 diabetes mellitus.

Association of coronary artery calcium with bone mineral density in postmenopausal women. Xu R1, Ni Yang H, Li YQ, Wang QF, Guo AH, Ayiti A, Chen XC, Gong R, Banu G, Dang Jian L, Gao Y, Sheng K, Maimti Y. Coron Artery Dis. 2016 Jun 29 Atherosclerosis and osteoporosis (OP) are common diseases in elderly individuals and may share common pathogenetic mechanisms. The aim of this study was to investigate the association between bone mineral density (BMD) and coronary artery calcium (CAC) inpostmenopausal women.

Suppression of glymphatic fluid transport in a mouse model of Alzheimer's disease. Peng W, Achariyar TM, Li B, Liao Y, Mestre H, Hitomi E, Regan S, Kasper T, Peng S, Ding F, Benveniste H, Nedergaard M, Deane R. Neurobiol Dis. 2016 Sep;93:215-25 Importantly, glymphatic failure preceded significant amyloid-? deposits, and thus, may be an early biomarker of AD. By extension, restoring glymphatic inflow and ISF clearance are potential therapeutic targets to slow the onset and progression of AD.

Sleep facilitates clearance of metabolites from the brain: glymphatic function in aging and neurodegenerative diseases. Mendelsohn AR, Larrick JW. Rejuvenation Res. 2013 Dec;16(6):518-23. Xie and colleagues now report that in mice the clearance activity of this so-called "glymphatic system" is strongly stimulated bysleep and is associated with an increase in interstitial volume, possibly by shrinkage of astroglial cells. Moreover, anesthesia and attenuation of adrenergic signaling can activate the glymphatic system to clear potentially toxic proteins known to contribute to the pathology of Alzheimer disease (AD) such as beta-amyloid (Abeta). Clearance during sleep is as much as two-fold faster than during waking hours.

Antibody against early driver of neurodegeneration cis P-tau blocks brain injury and tauopathy. Kondo A, Shahpasand K, Mannix R, Qiu J, Moncaster J, Chen CH, Yao Y, Lin YM, Driver JA, Sun Y, Wei S, Luo ML, Albayram O, Huang P,Rotenberg A, Ryo A, Goldstein LE, Pascual-Leone A, McKee AC, Meehan W, Zhou XZ, Lu KP. Nature. 2015 Jul 23;523(7561):431-6. Traumatic brain injury (TBI), characterized by acute neurological dysfunction, is one of the best

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known environmental risk factors for chronic traumatic encephalopathy and Alzheimer's disease, the defining pathologic features of which include tauopathy made of phosphorylated tau protein (P-tau). Treating TBI mice with cis antibody blocks cistauosis, prevents tauopathy development and spread, and restores many TBI-related structural and functional sequelae.

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Medical Epistemology esp as it effect clinical trials

From: vjp2@BioStrategist.com
Newsgroups: sci.med:556795
Subject: Med Epistemology (Bayes, Burke & Barzun)
Date: Sun, 14 Aug 2016
Message-ID: noqt49$ot7$1@reader2.panix.com

I have come to realise that what keeps science from spurious results is a priori encyclopedic knowledge. Two Anecdotes. When my dad was diagnosed with stomach cancer, I was told it was caused by nitrates in cold cuts. But when the cancer came back, as the Viagra Nobel showed nitric oxide to be the primordial mammalian neurotransmitter, I was told the 1930s theory of Helicobacter Pylori had been revived. In grand rounds a year ago, a young resident presented a case of an 89 yr old with enlarged heart as genetic, only to have an older doctor insist it was caused by 60 yrs of high blood pressure. I asked someone at the genome center and he said adding Bayesian priors to expert systems reduces spurious results. Bayes Law brought Kant's concept of a priori to mathematical probability. I have always felt uncomfortable with this concept of evidence based medicine precisely because every few years a totally new theory throws out all previous knowledge and makes new claims. Instead it pays to see why the old theory was wrong and to learn from our mistakes, not totally dismiss them. This really extends from the Hun or German peerless (hence uninspectable) hyperspecialist model of education which now seems to overtake the anglohellenistic model of peer reviewed encyclopedic (encyclios paideia) general education championed by Barzun. The peerless hyperspecialist might as well be a shaman or guru shrouded in mystery. I accept the errors of those who rejected Galileo, although you could argue they weren't based on scientific study but blind ideology, hence a different type of problem. I view ideology as the worship of human hueristics and the cause of atrocity when the heuristics take precedence to reality. I believe Burke's central thesis, that change should be measured and studied because if we replace everything at once, we will have nothing to stand on, or pulling the wrong thread could unravel the fabric. Further, as Sydney Hook warned, studying our old errors (or claptrap) keeps us from repeating them. Before "Japanese Innovation" we were taught that we should follow standards so we could continue to use old results, algorithms and equipment. As an example I learned electronic devices should be designed to handle (fan out) five accessories, but the modern ones reduced it the the bare minimum of one. Everything is now designed to only work in the short run, as if Keynes admonitions "In the long run, we are all dead" has been extended to science and engineering.

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Biofuels

For biofuels to succeed, they can't be ALMOST as good a gasoline (linear and aromatic alkanes with fewer than twelve carbons used in internal combustion) or diesel (larger alkanes used in external combustion, originally food oils transesterified with lye and methanol) but BETTER (refer to blending manuals preceding the current environmental and energy fads or for racing and you will find BTU/LB = 14.6 + 62(H -O/6) +4.05 S) Nitrogen enriched gasolene, nitroglycerin and rocket fuel show nitrogen bonds, esp rings, to be the most potent, albeit needing their toxicity and explosiveness mitigated. Ethanol production counterproductively destroys existing carbon bonds and ethanol attracts water which rusts engines. Past biofuel research has floundered when the price of oil fell (why not fund it countercyclically with automobile stocks?). Silage, sewage, landfill and sawdust provide the most economically sustainable source of biofuels. Cellulose is a sugar polymer but as its chirality is left-handed it cannot be digested by most animals. Fiberight.com will make ethanol from its unique garbage separation methods, probbly by shredding and washing as organics float. Plastics may be made more useful for fuel with cyclohexane, xylene, horseradish peroxidase and radiation. Westpheling (janetwest@uga.edu) has reengineered thermophilic C bescii to produce ethanol from switchgrass. Dumesic (dumesic@engr.wisc.edu) produces dimethyl furan by repeatedly dehydrating sugars with acid then hydrogenating them with a metal catalyst. Ditto Tomishige in Japan. This method has been speculated elsewhere to also work with ammonia in the presence of copper to turn sawdust into alkane. Ruan (ruanx001@umn.edu) produces diesel from sewage via algae. I would like to see the enzymes used by algae (typ chlorella minutissima, see jbenemman@aol.com) isolated and engineered to better take advantage of nitrogen bonds and accelarate production. Algae can also be used to recycle engine and factory (oxidant alkaline) scrubbing fluids used to capture carbon, nitrogen and sulfur compounds if there was a way to increase solar exposure surface area the way a heat exchanger exposes to heat. Reaction surface area is increased by flocculation. Garbage may also be gasified by steam or even plasma (Themelis njt1@columbia.edu, Filatov); flash heat has long been known to hydrogenate coal. Xylene depolymerises plastics. Venter has already gotten the algae to excrete the lipids so he can reuse the same algae repeatedly; His Synthetic Genomics was bought by Exxon. But it has also been suggested that E Coli might be more efficient for sewage (jdkeasling@lbl.gov keasling@berkeley.edu amyris.com khosla@stanford.edu); GlycosBio.com (ksan@rice.edu) got E coli to make isoprene from glycerol, and aschimer@ls9.com can make alkanes from E Coli Unifiedfuels.com will make alkanes from anything. Also try spyros.pavlostathis@ce.gatech.edu.