Submission of a 'Clinical-Trial-of-One' Proposal for Review, Critique and Discussion

An evidence based attempt to achieve cancer cell stasis via synergistic modulation of multiple cellular pathways (e.g. COX2, NF-κB, mevalonate, estrogen, and GADD45α & GADD45γ) utilizing medications that are readily available, and whose side effect profiles and toxicities are usually relatively benign, well understood and commonly managed.

Table of Contents

Objective

Extension of remission time for a Stage IV Ovarian Cancer patient via blockage of and/or retardation of the reproduction of cancer cells that survived and/or were generated by the chemotherapy series used to achieve remission.

Clinical History

CM is a 55 year old female who has completed 8 chemo cycles of a neoadjuvant treatment plan for Stage IV ovarian cancer, and who is now in remission. The chemotherapy agents used were carboplatin and docetaxel. Surgery occurred post cycle 4 and resulted in the removal of all visible tumor mass. At diagnosis, biopsy showed a tumor that expressed CK7, CK20, and WT1 and was negative for P16. Post surgery biopsy revealed tumor masses on both ovaries that appear to have been platinum/taxol sensitive – with those tumors being largely necrotic. A second tumor type of approximately one centimeter was found on one of the fallopian tubes, and this tumor appeared to be resistant to the chemo regimen as it was found to be 100% viable. The phenotype of this tumor has not been characterized.

Strategy

This regimen will attempt to utilize currently available medications to safely impact cellular pathways that uniquely drive or enable the progression of cancer cells, with one set of pathways being unique to many gynecological and breast cancers.

The patient's safety and wellbeing will remain the highest priority.

The agents that will be utilized have been recommended by a clinical pharmacist based on his professional judgment after an in-depth review of a combination of experimental and clinical evidence that has been data-mined from the literature, and which suggests a reasonable probability of success.

These recommendations and the reasoning behind them have been discussed with the patient and the patient's physician, and have been modified as appropriate based on those discussions. All actions taken with regard to this protocol will be communicated with the patient's physician prior to implementation, and no actions will be taken without his concurrence.

Although the dosages of the agents that will be used may tend to be at the high end of currently accepted doses, they will fall within those currently used to safely treat other indications - and will be appropriately scaled to the patient's physical parameters. Additionally, doses will be slowly titrated and patient response will be closely monitored to avoid medication misadventures.

The pathways that will be targeted include NF-κB, Gadd45α/Gadd45γ and those impacted by COX2 and Estrogen.
The regimen will consist of a baseline regimen coupled with a 'burst' regimen of limited duration that will be periodically implemented.

Regimen Recommendations

Included in this regimen are agents that should be administered on a continuous basis and agents that may be more safely utilized over short periods of time on a periodic basis. The agents that should be administered on an intermittent basis have therefore been allocated to periodic short term administration schedules – or 'bursts'. The agents proposed at this time for both the continuous and 'burst' parts of this protocol have been detailed below.

Continuous (Baseline) Agents –

These medications will be given daily, and their dosages are not expected to vary.

Targeted Pathway	Therapeutic Class	Agent	Dose	Frequency
COX2	NSAID	**Aspirin**	**325 mG**	**Twice a Day**
Estrogen	**Aromatase Inhibitor**	**Physician's Choice**		

'Burst' Agents –

These medications will be titrated to target dosages as tolerated over a period of 2-3 weeks and will continue after titration for a period of two weeks, after which they will be stopped until the next cycle. At this time it is believed that the 'bursts' will occur every 4 months.

Targeted Pathway	Therapeutic Class	Agent	Target Dose	Frequency
NF-κB	NSAID	**Salsalate**	**1500 mG**	**Twice a Day**
Mevalonate	Statin	**Lipitor® (atorvastatin)**	**80 mG**	**Daily**
GADD45α & GADD45γ	Will rely on salicylate from the salsalate dose to impact this pathway. If cancer appears to be reoccurring it is recommend that either diclofenac or sulindac be added to the regimen to more aggressively impact this pathway. Finasteride is a non-NSAID option that should be seriously considered if diclofenac or sulindac are contemplated. Finasteride would make an aromatase inhibitor mandatory.			

Most Likely Regimen Modifications –

In case an agent proves unacceptable or loss of remission appears to be occurring the following therapeutic interchanges should be considered.

1. **If chemotherapy is re-initiated this regimen must be reevaluated.** It is believed that NSAID levels sufficient to impact the NF-κB pathway at chemotherapy infusion will significantly impair the action of platinum based chemo agents, but are appropriate 48 hours post chemotherapy.[16] Additionally, aspirin at any dose would be a poor choice in patients with impaired platelet production.
2. The pulse dose of salsalate could be replaced with a titration of aspirin to a target dose of 5.4 grams per day delivered in 4-5 doses as tolerated. (note: 5.4 grams is the commonly accepted max daily dose)
3. Any lipophilic statin could be used in lieu of atorvastatin as long as the target dose is set at the agent adjusted dose for artherosclerosis reversal.
4. If the COX2 aspirin dosing is unacceptable meloxicam or celebrex are the recommended alternatives.
5. **If loss of remission appears to be occurring the following actions are recommended –**

a. Replace the 'pulse' phase's salsalate with aspirin at a target dose of 7 grams per day divided into 4-5 doses. (the baseline regimen's COX2 aspirin dose should be counted as part of this daily target dose)
b. Add diclofenac or sulindac to the regimen's 'burst' phase to more aggressively attempt to impact the GADD45α & GADD45γ pathways.
c. Consider adding finasteride 5-10 mG three times per day as a non-NSAID alternative to diclofenac or sulindac for the GADD45α & GADD45γ pathways. Its use would require co-administration of an aromatase inhibitor.

IMPORTANT –

1. The target salsalate dose will vary as a function of gender, height, and weight. The dose has to be titrated on an individual basis.
2. Never give high dose finasteride to cancer cells that are stressed or damaged. The pathways it works on enhance cell damage repair when the cells are stressed, and it is believed this will actually reduce cancer cell kill rates.

Supporting Rationale

It is extremely difficult to kill all cancer cells with chemotherapy protocols. The surviving cells will continue to grow and generate new tumor masses if they're allowed to. These tumors are likely to be spread throughout the body, and to be resistant to previously used chemotherapy agents. Additionally, chemotherapy regimens – particularly those that attack DNA (e.g. platinum based agents) can generate new neoplasms.

Thus, it is desirable to impair these cancer cells' growth and/or to catalyze their death. However, cancer cells are difficult to selectively kill. This regimen targets cellular processes that are uniquely unregulated in cancer cells and attempts to bring them into a state of regulation that will slow their growth or enable them to recognize the need to enter apoptosis.

NF-κB is one of the pathways that this protocol targets. Many NSAIDs are capable of impacting this pathway, and of inhibiting cancer cell growth and/or inducing apoptosis. But, translation of this property to humans is challenging because it is difficult to safely achieve free plasma concentrations that are sufficient to elicit the desired effect because of drug metabolism, associated toxicities, and plasma protein binding.

Salicylate based NSAIDs (aspirin and salsalate) are pharmacokinetically unique in that their metabolism and plasma protein binding is saturable – thus enabling the generation of significant free plasma levels. It is known that the levels that are safely achievable are sufficient to impact NF-κB as the result of

studies into their ability to shut down cellular crosstalk from the NF-κB pathway to insulin receptors.[1-7, 63-64]

The selective-COX2-inhibitor celecoxib also appears to be capable of impacting NF-κB, but it shares the metabolism and protein binding limitations the NSAIDs have. However, it is capable of impacting this pathway at much lower concentrations than the NSAIDs do. It appears probable that this is the basis for its ability to impact colorectal adenomas and adenomatous polyps at twice daily 400 mG doses.[13, 15, 21] Despite an impressive body of evidence supporting its ability to impact cancer growth and propagation it was not chosen as the primary agent for NF-κB impact because of its questionable status relative to cardiovascular events and physicians' reluctance to use it because of those questions.

COX-2 seems to be associated with tumor metastasis. There are many agents that can suppress its influence. The ones considered for this protocol include normal dose aspirin, low dose celebrex, and max dose meloxicam. Celebrex and meloxicam have fewer gastrointestinal side effects because of their selectivity for COX-2 over COX-1. Any one of these three agents would have been a good choice. Ultimately aspirin was chosen.

There remains significant controversy over why statins are capable of slowing tumor growth and/or inducing tumor cell apoptosis.[41-47] However, there is significant evidence that concurrent exposure to NSAIDs or selective-COX2-inhibitors and statins significantly lowers the concentrations required to induce apoptosis for both the statin and the NSAID/selective-COX2-inhibitor.[18, 20, 22] Although statins are also limited by metabolism and protein binding issues, it is hoped that sufficient synergism will be achieved by the addition of hydrophobic statins to this regimen.

Estrogen receptors are reported to drive the growth and progression of many ovarian cancer tumors. In fact, it is reported that > 90% of confirmed ovarian cancers have lost their progesterone receptors' function. This allows unopposed estrogen receptor stimulation of the tumor's cells, and it has been reported that > 80% have retained their estrogen receptors' functionality.[74] Thus, it appears mandatory to incorporate an agent into this protocol to block the effect of estrogen on estrogen receptors. Aromatase inhibitors appear to retain their functionality longer than estrogen receptor blockers, and are reported to be better tolerated by patients. Selection of the agent from this category will be left to the patient's physicians, as they are undoubtedly more familiar with the tradeoffs that must be considered to make this recommendation.

The Gadd45α & Gadd45γ pathways are reported to be obligate to apoptosis escape. Among the substances that can impact them are several NSAIDs - with sulindac sulfide, finasteride, diclofenac, flurbiprofen (probably R-flurbiprofen), and sulindac sulfone being among the agents that exert the strongest effect. It is worthy of note that – although several different reasons have been proposed –

these agents are repeatedly reported in journal articles as being among the top inducers of cancer cell apoptosis. Aspirin (and by extension, salicylate) also impacts this pathway, but is not nearly as powerful as the aforementioned agents. But - once again - the problems of metabolism, protein binding, and toxicity rear their ugly heads. Other than aspirin, it remains unclear that - for the NSAIDs - sufficient plasma concentrations can be attained before unacceptable side effects arise. Finasteride, on the other hand, is an extremely interesting medication. It has metabolism and protein binding problems just like the others, but it is a powerful agent and its toxicity profile may allow it to be used for short periods of time at much higher doses than what are currently used to reverse BPH or for blocking hormone stimulation of prostate cancer.[67-69] The caveat for this medication, though, is that by inhibiting the metabolism of testosterone it appears the body is driven to generate more estrogen. Thus, if this agent is to be used for the treatment of a gynecological or breast cancer co-administration of an aromatase inhibitor would be mandatory.

Although PPAR-γ was also considered as a potential target, thalidomide was the only agent capable of impacting PPAR-γ that was believed to be safe enough to incorporate into this protocol. It was ultimately decided that there was not enough time to appropriately research this agent before the protocol would be needed, and that its previous controversies would stretch the patient's physician's ability to buy-in to supporting this effort to the breaking point.

References

1. M. Yuan, N Konstantopoulos, J. Lee, L. Hanson, Z. Li, M. Kafin, S. E. Shoelson 2001. **Reversal of Obesity – and Diet-Induced Insulin Resistance with Salicylates or Targeted Disruption of Ikkβ.** *Science* 293: 1673-1673.
2. J. K. Kim, Y. Kim, J. J. Fillmore, Y. Chen, I. Moore, J. Lee, M. Yuan, Z.W. Li, M. Karin, P. Perret, S. E. Shoelson, G. I. Shulman 2001. **Prevention of fat-induced insulin resistance by salicylate.** *The Journal of Clinical Investigation* 108: 437-446.
3. M. J. Birnbaum 2001. **Turning down insulin signaling.** *The Journal of Clinical Investigation* 108: 655-659.
4. C. N. Serhan. E Oliw 2001. **Unorthodox routes to prostanoid formation: new twists in cyclooxygenase-initiated pathways.** *The Journal of Clinical Investigation* 107:12 1481-1489.
5. M. G. Netea, C. J. Tack, P. M. Netten, J. A. Lutterman, J. W. M. Van der Meer 2001. **Letters to the Editor – The effect of salicylates on insulin sensitivity.** *The Journal of Clinical Investigation* 108:11 1723-1724.
6. R. S. Hundal, K. F. Petersen, A. B. Mayerson, P. S. Randhawa, S. Inzucchi, S. E. Shoelson, G. I. Shoelson 2002. **Mechanism by which high-dose aspirin improves glucose metabolism in type 2 diabetes.** *The Journal of Clinical Investigation* 109:10 1321-1326.
7. S. E. Shoelson, J. Lee, A. B. Goldfine 2006. **Inflammation and insulin resistance.** *Journal of Clinical Investigation* 116:7 1793-1801.
8. C. N. Serhan, C. B. Clish 2000. **Aspirin triggered lipid mediators: novel inhibitors of leucocyte trafficking.** *Thorax* 55: S10-S12.
9. Z. Gao, A. Aamir, M. J. Quon, Z. Dong, J. Ye 2003. **Aspirin Inhibits Serine Phosphoylation of InsulinReceptor Substrate 1 in Tumor Necrosis Factor-treated Cells through Targeting Multiple Serine Kinases.** *The Journal of Biological Chemistry 278:27 24944-24950.*
10. S. Endres, R. E. D. Whitaker, R. Ghorbani, S. N. Meydani, C. A. Dinarello 1996. **Oral aspirin and ibuprofen increase cytokine-induced synthesis of IL-1β and of tumor necrosis factor-α *ex vivo*.** *Immunology* 87: 264-270.
11. I. Tegeder, J. Pfeilschifter, G. Geiaalinger 2001. **Cyclooxygenase-independent actions of cyclooxygenase inhibitors.** *FASEB J.* 15: 2057-2072.
12. J. M. Bock, S. G. Menon, P. C. Goswami, L. L. Sinclair, N. S. Bedford, F. E. Domann, D. K. Trask 2007. **Relative Non-Steroidal Anti-Inflammatory Drug (NSAID) Antiproliferative Activity is Mediated Through p21-Induced G1 Arrest and E2F Inhibition.** *Molecular Carcinogenesis* 46: 857-864.
13. P. Andrews, X. Zhao, J. Allen, F. Li, M. Chang 2008. **A comparison of the effectiveness of selected non-steroidal anti-inflammatory drugs and their derivatives against cancer cells in vitro.** *Cancer Chemother Pharmacol* 61: 203-214.

14. S. Grosch, I. Tegeder, E. Niederberger, L. Brautigam, G. Geisslinger 2001. **COX-2 independent induction of cell cycle arrest and apoptosis in colon cancer cells by the selective COX-2 inhibitor celcoxib.** *FASEB Journal 15:14 2742-2744.*
15. N. M. Davies, A. J. McLachlan, R. O. Day, K. M. Williams 2000. **Clinical Pharmacokinetics and Pharmacodynamics of Celecoxib.** *Clin Pharmacokinet* 38:3 225-242.
16. M. N. A. Bijman, C. A. Hermelink, M. P. A. van Berkel, A. C. Laan, M. L. Janmaat, G. J. Peters, E. Boven 2008. **Interaction between celecoxib and docetaxel or cisplatin in human cell lines of ovarian cancer and colon cancer is independent of COX-2 expression levels.** *Biochemical Pharmacology* 75: 427-437.
17. Y. Song, S. Kim, Y. Juhnn, Y. Song 2007. **Apoptotic Effect of Celecoxib Dependent Upon p53 Status in Human Ovarian Cancer Cells.** *Ann N.Y. Acad Sci* 1095: 26-34
18. H. Xiao, Q. Zhang, Y. Lin, B. S. Reddy, C. S. Yang 2008. **Combination of atorvastatin and celecoxib synergistically induces cell cycle arrest and apoptosis in colon cancer cells.** *Int J Cancer* 122: 2115-2124.
19. M. Jalving, J. J. Koornstra, S. De Jong, E. G. E. De Vries, J. H. Kleibeuker 2005. **Review article: the potential of combinational regimen with non-steroidal anti-inflammatory drugs in the chemoprevention of colorectal cancer.** *Aliment Pharmacol Ther* 21: 321-339.
20. H. Xiao, C.S. Yang 2008. **Mini Review – Combination regimen with statins and NSAIDs: A promising strategy for cancer chemoprevention.** *Int J Cancer* 123: 983-990.
21. T. J. Maier, K. Schilling, R. Schmidt, G. Geisslinger, S. Grosch 2004. **Cyclooxygenase-2 (COX-2)-dependent and –independent anticarcinogenic effects of celecoxib in human colon carcinoma cells.** *Biochemical Pharmacology* 67: 1469-1478.
22. B. S. Reddy, C. X. Wang, A. Kong, T. O. Khor, X. Zheng, V. E. Steele, L. Kopelovich, C. V. Rao 2006. **Prevention of Azoxymethane –Induced Colon Cancer by Combination of Low Doses of Atorvastatin, Aspirin, and Celecoxib in F 344 Rats.** *Cancer Res* 66:8 4542-4546.
23. A. R. Munkarah, R. Ali-Fehmi, J. Z. Jiang, E. Elhammady, J. M. Malone Jr, G. M. Saed 2007. **The effects of combining docetaxel and cyclooxygenase-2 inhibitors on proliferation and apoptosis in epithelial ovarian cancer.** *Anti-Cancer Drugs* 18:8 889-896.
24. A. T. Chang, S. Ogino, C. S. Fuchs 2009. **Aspirin Use and Survival After Diagnosis of Colorectal Cancer.** *JAMA 302:6 649-658.*
25. B. Xin, Y. Yokoyama, T. Shigeto, H. Mizunuma 2007. **Anti-Tumor Effect of Non-Steroidal Anti-Inflammatory Drugs on Human Ovarian Cancers.** *Pathology Oncology Research* 13:4 365-369.
26. M. A. Kern, M. M. Schoneweib, D. Sahi, M. Bahlo, A. M. Haugg, H. U. Kasper, H. P. Dienes, H. Kaferstein, K. Breuhahn, P. Schirmacher 2004. **Cyclooxygenase-2 inhibitors suppress the growth of human hepatocellular carcinoma implants in nude mice.** *Carcinogenesis* 25:7 1193-1199.
27. T. Naruse, Y. Nishida, K. Hosono, N. Ishiguro 2006. **Meloxicam inhibits osteosarcoma growth, invasiveness and metastasis by COX-2-dependent and independent routes.** *Carcinogenesis* 27:3 584-592.

28. G. A. Piazza, A. K. Rahm, T. S. Finn, B. H. Fryer, H. Li, A. L. Stoumen, R. Pamukcu, D. J. Ahnen 1997. **Apoptosis Primarily Accounts for the Growth-Inhibitory Properties of Sulindac Metabolites and Involves a Mechanism That Is Independent of Cyclooxygenase Inhibition, Cell Cycle Arrest, and p53 Induction.** *Cancer Research* 57: 22452-2459.
29. B. S. Reddy, T. Kawamori, R. A. Kawamori, R. A. Lubet, V. E. Steele, G. J. Kelloff, C. V. Rao 1999. **Chemopreventive Efficacy of Sulindac Sulfone against Colon Cancer Depends on time of Administration during Carcinogenic Process.** *Cancer Research* 59: 3387-3391.
30. R. S. Bresailier, et. al. 2005. **Cardiovascular Events Associated with Rofecoxib in a Colorectal Adenoma Chemoprevention Trial.** *N Engl J Med* 352: 1092-1102.
31. C. Ruegg, J. Zaric, R. Stupp 2003. **Non steroidal anti-inflammatory drugs and COX-2 inhibitors as anti-cancer therapeutics: hypes, hopes and reality.** *Annals of Medicine* 35: 7 476-487.
32. C. H. Lee, Y. Jeon, S. Kim, Y. Song 2007. **NF-κB as a potential molecular target for cancer therapy.** *BioFactors* 29: 19-35.
33. H. J. Kim, N. Hawke, A. S. Baldwin 2006. **NF-κB and IKK as therapeutic targets in cancer.** *Cell Death and Differentiation* 13: 738-747.
34. J. Luo, H. Kamata, M. Karin 2005. **IKK/NF-κB signaling: Balancing life and death – a new approach to cancer therapy.** *The Journal of Clinical Investigation* 115: 10 2625-2632.
35. S. Hernandez-Diaz, L. A. Garcia-Rodriguez 2001. **Epidemiologic Assessment of the Safety of Conventional Nonsteroidal Anti-Infammatory Drugs.** *Am J Med 110(3A):20S-27S.*
36. C. V. Rao, B.S. Reddy 2004. **NSAIDs and Chemoprevention.** *Current Cancer Drug Targets* 4: 29-42.
37. A. Whelton 2001. **Renal Aspects of Treatment with Conventional Nonsteroidal Anti-Inflammatory Drugs Versus Cyclooxygenase -2-Specific Inhibitors.** *The American Journal of Medicine* 110:3A 33S-42S.
38. K. M. Starko 2009. **Salicylates and Pandemic Influenza Mortality, 1918-1919 Pharmacology, Pathology, and Historic Evidence.** *CID* 49: 000-000.
39. L. G. Raisz 2001. **Potential Impact of Selective Cyclooxygenase-2 Inhibitors on Bone Metabolism in Health and Disease.** *The American Journal of Medicine* 110(3A):43S-45S.
40. F. Catella-Lawson, L. J. Crawford 2001. **Cyclooxygenase Inhibition and Thrombogenicity.** *The American Journal of Medicine* 110(3A): 28S-32S.
41. R. G. Elmore, Y. Ioffe, D. R. Scoles, B. Y. Karlan, A. J. Li 2008. **Impact of statin therapy on survival in epithelial ovarian cancer.** *Gynecologic Oncology* 111: 102-105.
42. H. Liu, S. Liang, S. Kumar, C. M. Weyman, W. Liu, A. Zhou 2009. **Statins induce apoptosis in ovarian cancer cells through activation of JNK and enhancement of Bim expression.** *Cancer Chemother Pharmacol* 63: 997-1005.
43. O. Yu, D. M. Boudreau, D. S. M. Buist, D. L. Miglioretti 2008. **Statin use and female reproductive organ risk in a large population-based setting.** *Cancer Causes Control* November 2008.

44. S. Kaneta, K. Satoh, S. Kano, M. Kanda, K. Ichihara 2003. **All hydrophobic HMG-CoA reductase inhibitors induce apoptotic death in rat pulmonary vein endothelial cells.** *Artherosclerosis* 170:237-243.
45. R. H. Stern, B. Yang, N. J. Hounslow, M MacMahon, R. B. Abel, S. C. Olson 2000. **Pharmacodynamics and pharmacokinetic-pharmacodynamic relationships of atorvastatin, an HMG-CoA reductase inhibitor.** *J Clin Pharmacol 40: 616-623.*
46. E. A. Collisson, C. Kleer, M. Wu, A. De, S. S. Gambhir, S. D. Merajver, M.s. Kolodney 2003. **Atorvastatin prevents RhoC isoprenylatin, invasion, and metastasis in human melanoma cells.** *Molecular Cancer Therapeutics* 2: 941-948.
47. S. A. Holstein, H. R. Knapp, G. H. Clamon, D. J. Murry, R. J. Hohl 2006. **Pharmacodynamic effects of high dose lovastatin in subjects with advanced malignancies.** *Cancer Chemother Pharmacol 57: 155-164.*
48. G. F. O'Malley 2007. **Emergency Department Management of the Salicylate-Poisoned Patient.** *Emerg Med Clin N Am* 25: 333-346.
49. P. I. Dargan, C. I. Wallace, A. L. Jones 2002. **An evidence based flowchart to guide the management of acute salicylate (aspirin) overdose.** *Emer Med J* 19: 206-209.
50. P. A. Chyka, A. R. Erdman, G. Christianson, P. M. Wax, L. L. Booze, A. S. Manoguerra, E. M. Caravati, L. S. Nelson, K. R. Olson, D. J. Cobaugh, E. J. Scharman, A. D. Woolf, W. G. Troutman 2007. **Salicylate poisoning : An evidence-based consensus guideline for out-of-hospital management.** *Clinical Toxicology* 45: 95-131.
51. S. L. Greene, P. I. Dargan, A. L. Jones 2005. **Acute Poisoning: Understanding 90% of cases in a nutshell.** *Postgrad Med J* 81: 204-216.
52. S. A. Holstein, H. r. Knapp, G. H. Clamon, D. J. Murry, R. J. Hohl 2007. **Erratum – Pharmacodynamic effects of high dose lovastatin in subjects with advanced malignancies.** *Cancer Chemother Pharmacol* 59: 559.
53. P. Anand, C. Sundaram, S. Jhurni, A. B. Ajaikumar, B. Kunnumakkara, B. B. Aggarwal 2008. **Curcumin and cancer: An 'old-age' disease with an 'age-old' solution.** *Cancer Letters* 267: 133-164.
54. F. Buttgereit, G. R. Burmester, L. S. Simon 2001. **Gastrointestinal Toxic Side Effects of Nonsteroidal Anti-Inflammatory Drugs and Cyclooxygenase-2-Specific Inhibitors.** *Am J Med* 110(3A): 13S-19S.
55. J. Rhode, S. Fogoros, S. Zick, H. Wahl. K. A. Griffith, J. Huang, J. R. Liu 2007. **Ginger inhibits cell growth and modulates angiogenic factors in ovarian cancer cells.** *BMC Complementary and Alternative Medicine* 7: 44-53.
56. B. H. Ali, G. Blunden, M. O. Tanira, A. Nemmar 2008. **Some phytochemical, pharmacological, and toxicological properties of ginger (*Zingiber officinale* Roscoe): A review of recent research.** *Food and Chemical Toxicology* 46: 409-420.

57. F. Bayram, I. I. Muderris, M. Guven, F. Kelestimur 2002. **Comparison of high-dose finasteride (5mg/day) versus low-dose finasteride (2.5mg/day) in the treatment of hirsutism.** *European Journal of Endocrinology* 147: 467-471.
58. DRUGDex Evaluations – Diclofenac. Micromedex Healthcare Series.
59. DRUGDex Evaluations – Finasteride. Micromedex Healthcare Series.
60. DRUGDex Evaluations – Meloxicam. Micromedex Healthcare Series.
61. DRUGDex Evaluations – Sulindac. Micromedex Healthcare Series.
62. DRUGDex Evaluations – Celecoxib. Micromedex Healthcare Series.
63. Z. T. Bloomgarden 2003. **Inflammation and Insulin Resistance.** *Diabetes Care* 26:5 1619-1623.
64. A. Fleischman, R. Bernier, S. E. Shoelson, A. B. Goldfine 2008. **Salsalate Improves Glycemia and Inflammatory Parameters in Obese Young Adults.** *Diabetes Care* 31: 2 289-294.
65. S. M. Zick, Z. Djuric, M. T. Ruffin, A. J. Litzinger, D. P. Normolle, A. Alrawi, M. R. Feng, D. E. Brenner 2008. **Pharmacokinetics of 6-Gingerol, 8-Gingerol, 10-Gingerol, and 6-Shogaol and Conjugate Metabolites in Healthy Human Subjects.** *Cancer Epidemiol Biomarkers Prev* 17:8 1930-1936.
66. R. L. Thangapazham, A. Sharma, R. K. Maheshwari 2006. **Multiple Molecular Targets in Cancer Chemoprevention by Curcumin.** *The AAPS Journal* 8:3 Article 52 E443-E449.
67. A. Cretu, X. Sha, J. Tront, B. Hoffman, D. A. Liebermann 2009. **Stress sensor Gadd45 genes as therapeutic targets in cancer.** *Cancer Ther* 7(A): 268-276.
68. L. F. Zerbini, T.A. Liberman 2005. **Life and Death in Cancer.** *Cell Cycle* 4:1 18-20.
69. L. F. Zerbini, A. Czibere, Y. Wang, R. G. Correa, H. Otu, M. Joseph, Y. Takayasu, M. Silver, X. Gu, K. Ruchusatsawat, L. Li, D. Sarkar, J. Zhou, P. B. Fisher, T. A. Liberman 2006. **A Novel Pathway Involving Melanoma Differentiation Associated Gene-7/Interleukin-24 Mediates Nonsteroidal Anti-inflammatory Drug-Induced Apoptosis and Growth Arrest of Cancer Cells.** *Cancer Res* 66:24 11922-11931.
70. L. S. Mitchell 2006. **Drug Information Response – 'What is the effect (including MOA of NSAIDs on glucose and lipid parameters?'. Private Copy**
71. D. J. Hassndelsman. Endotext.org. Chapter 2 – Androgen **Physiology, Pharmacology and Abuse.** http://www.endotext.org/male/male2/male2.htm .
72. Estrogen Pathway
73. T. C. Hamilton, R. C. Young, W. M. McKoy, K. R. Grotzinger, J. A. Green, E. W. Chu, J. Whang-Peng, A. M. Rogan, W. R. Green, R. F. Ozols 1973. **Characterization of a Human Overian Carcinoma Cell Line (NIH:OVDCAR-3) with Androgen and Estrogen Receptors.** *Cancer Research* 43: 5379-5389.
74. S. Ho 2003. **Review - Estrogen, Progesterone and Epithelial Ovarian Cancer.** *Reproductive Biology and Endocrinology* 1:73 1-8.
75. N. M. Davies, N. M. Skjodt 1999. Clinical Pharmacokinetics of Meloxicam**.** *Clin Pharmacokinet* 36:2 115-126.

76. I. M. Thompson, C. M. Tangen, P. J. Goodman, M. S. Lucia, E. A. Klein 2009. **Chemoprevention of Prostate Cancer.** *The Journal of Urology* 182: 499-508.
77. J. R. Carlin, P. Hoglund, L.-O. Eriksson, P. Christofalo, S. L. Gregoire, A. M. Taylor, K. –E. Andersson 2002. **Disposition and Pharmacokinetics of [^{14}C]Finasteride After Oral Administration In Humans.** *Drug Metabolism and Disposition* 20:2 148-155.
78. A. B. Reed, D. J. Parekh 2009. **The utility of 5-α reductase inhibitors in the prevention and diagnosis of prostate cancer.** *Current Opinion in Urology* 19: 238-242.
79. J. F. Thorpe, S. Jain, T. H. Marczylo, A. J. Gescher, W. P. Steward, J. K. Mellon 2007. **A review of phase III clinical trials of prostate cancer chemoprevention.** *Ann R Coll Surg Engl* 89: 207-211.
80. A. Cretu, X. Sha, J. Tront, B. Hoffman, D. A. Liebermann 2009. **Stress sensor Gadd45 genes as therapeutic targets in cancer.** *Cancer Ther* 7(A): 268-276.
81. W. N. William Jr, J. V. Heymach, E. S. Kim, S. M. Lippman 2009. **Molecular targets for cancer chemoprevention.** *Nature Reviews – Drug Discovery* 8: 213-225.
82. DRUGDex Evaluations – Atorvastatin. Micromedex Healthcare Series.
83. DRUGDex Evaluations – Lovastatin. Micromedex Healthcare Series.
84. DRUGDex Evaluations – Simvastatin. Micromedex Healthcare Series.
85. POISONDex Evaluations – Finasteride. Micromedex Healthcare Series.
86. POISONDex Evaluations – Lovastatin and Related Drugs. Micromedex Healthcare Series.
87. POISONDex Evaluations – Nonsteroidal Antiinflammatory Drugs. Micromedex Healthcare Series.
88. POISONDex Evaluations – Salicylates. Micromedex Healthcare Series.
89. M. Yin, Y. Yamamoto, R. B. Gaynor 1998. **Letters to Nature – The anti-inflammatory agents aspirin and salicylate inhibit the activity of IκB kinase-β.** *Nature* 396:5 77-80.
90. G. Levy, L. E. Hollister 1964. **Variation in Rate of Salicylate Elimination by Humans.** *Brit Med J* 2: 286-288.
91. S. Su, C. Chou, C. Kung, J. Huang 2003. **In vitro and in vivo comparison of two diclofenac sodium sustained release oral formulations.** *International Journal of Pharmaceutics* 260: 39-46.
92. R. Khosravan, J. Wu, N. Joseph-Ridge, L. Vernillet 2006. **Pharmacokinetic Interactions of Concomitant Administration of Febuxostat and NSAIDs.** *J Clin Pharmacol* 46: 855-866
93. G. F. Ray, R. C. Lanman, C. J. Fu, N. S. Paranka, R. Pamukcu, s. C. Wheeler 1995. **Determination of FGN-1 (an active metabolite of sulindac) in human plasma, urine, and feces by HPLC.** *Journal of Pharmaceutical and Biomedical Analysis* 14: 213-220.
94. M. Schachter 2004. **Chemical, pharmacokinetic and pharmacodynamic properties of statins: an update.** *Fundamental & Clinical Pharmacology* 19: 117-125.
95. S. Bellosta, R. Paoletti, A. Corsini 2004. **Safety of Statins: Focus on Clinical Pharmacokinetics and Drug Interactions.** *Circulation* 109: III-50 – III-57.
96. A. Corsini, S. Bellosta, R. Baetta, R. Fumagalli, R. Paoletti, F. Bernini 1999. **New insights into the pharmacodynamic and pharmacokinetic properties of statins.** *Pharmacology & Therapeutics* 84: 413-428.

97. S. E. Nissen, S. J. Nicholls, I. Sipahi, P. Libby, J. S. Raichlen, C. M. Ballantyne, J. Davignon, R. Erbel, J. C. Fruchart, J. C. Tardif, P. Schoenhagen, T. Crowe, V. Cain, K. Wolski, M. Goormastic, E. M. Tuzcu 2006. **Effect of Very High-Intensity Statin Therapy on Regression of Coronary Artherosclerosis – The ASTEROID Trial.** *JAMA* 295:13 1556-1565.
98. A. S. Wierzbicki, P. J. Lumb, Y. K. Semra, M. A. Crook 1998. **High-dose atorvastatin therapy in severe heterozygous familial hypercholesterolaemia.** *Q J Med* 91: 291-294.
99. P. P. Toth 2008. **High-dose statin therapy: Benefits and safety in aggressive lipid lowering.** *Supplement to The Journal of Family Practice* 57:5 S29-S36.
100. R. E. Harris. **COX-2 Blockage in Cancer Prevention and Therapy** (Cancer Drug Discovery and Development) 2003 Humana Press
101. W. C.Evans. **Trease and Evans Pharmacognosy** 15th Edition 2002 W. B. Saunders