

# **OFF LABEL PHARMACEUTICAL 'COCKTAILS' FOR CANCER TREATMENT**

A4M Integrative Cancer Therapies

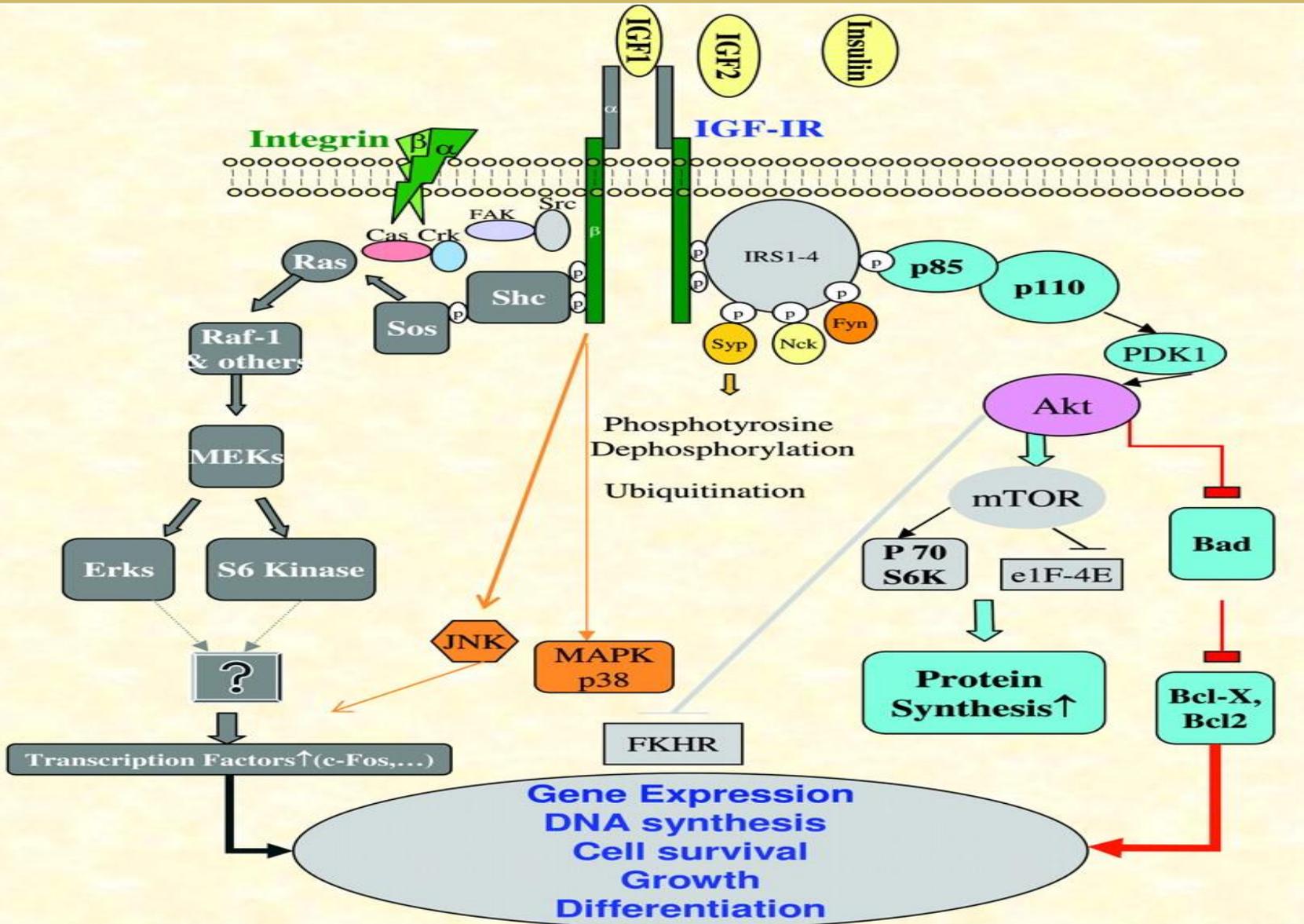
Module 6

June 6-8, 2013

# Metformin (↕AMPK ↕IGF-1 &c-MYC) (↕mTOR)

- Metformin: elicits anticancer effects through the sequential modulation of DICER and c-MYC. *Nat Commun.* 2012 May 29;3:865. doi: 10.1038/ncomms1859.
- Is synthetically lethal with glucose withdrawal in cancer cells. *Cell Cycle.* 2012 Aug 1;11(15):2782-92. Epub 2012 Aug 1.
- Potentiates the effects of paclitaxel in endometrial cancer. *Gynecologic Oncology* 125 (2012) 458–469
- Together with the mTOR inhibitor everolimus (Affinitor) sensitize breast cancer cells to the cytotoxic effect of chemotherapeutic drugs. *Anticancer Res.* 2012 May;32(5):1627-37.
- Inhibits P-glycoprotein expression via the NF-κB pathway through AMPK activation. *Br J Pharmacol.* 2010 Nov 3. doi: 10.1111/j.1476-5381.2010.01101.x.

# IGF-IR Signaling Pathway



# Metformin in cancer prevention

- Dr. Dario Alessi's research (U. of Dundee) involving data from patient records over ten years, have shown that patients on metformin showed anywhere between a 30-40% protection against all forms of cancer, compared to diabetics not on metformin. Diabetics on metformin show lower cancer incidence than non-diabetics.

# Metformin candidates

- Metformin can be safely given as an off-label adjunctive treatment in cancer patients, especially breast, ovarian, colorectal, prostate, pancreas and perhaps in glioma patients who have Type 2 diabetes, metabolic syndrome, elevated circulating insulin levels, or are obese, or even simply those who cannot or do not adhere to a low carb low fat diet.

# Gossypol

- Polyphenolic compound from seeds, stem, and roots of cotton plant, being developed as a male contraceptive. Available thru compounding pharmacies.
- Anti-cancer activity in animals reported from Russia in the 1960s

# Gossypol (cont'd)

- Gossypol promotes apoptosis of breast, bladder, lymphoma, leukemia (CML and CLL), myeloma, prostate, colorectal, alveolar cell lung, glioma, pancreas, melanoma, nasopharyngeal, and head and neck squamous cell cancers. A preponderance of the research reported on efficacy against hematologic cancers and prostate cancer.

Gossypol, a natural BH3 mimetic, is a small-molecule inhibitor of Bcl-2/Bcl-xL/Mcl-1,

inhibition of the antiapoptotic protein Bcl-xL accompanied by an increase of proapoptotic Noxa and Puma (Meng Y, et al. *Mol Cancer Ther*, 7:7, pp. 2192-2202, 2008).

Gossypol may exert its apoptotic effects via downregulated expression of NF-kappaB-regulated gene products, including inhibitor of apoptosis protein IAP-1, IAP-2, and X-linked IAP (Moon DO, et al. *Cancer Lett* 264:2, pp.192-200, 2008).

--also a protein kinase C inhibitor.

# Gossypol Clinical evidence

- long-term clinical remission of a patient with chronic lymphocytic leukemia using gossypol was reported. (Politzer, *Phytomedicine* 15:8, pp. 563-5, 2008)
- Gossypol is currently the only orally bioavailable pan-Bcl-2 inhibitor under clinical investigation.

In the US, phase I/II clinical trials are currently ongoing or planned with gossypol under the product code "AT-101" by [Ascenta Therapeutics](#) as an adjuvant therapy for human prostate cancer. A small trial of the product in 23 men with prostate cancer who were chemo-naive but had rising PSA and who took 30mg of product for 21 out of 28 days over 20 to 24 weeks noted decreases in PSA parameters in some. 5 out of the 23 patients had to discontinue the drug because of gastrointestinal side-effects (ileus). In 2009, Ascenta also presented preliminary data indicating that AT-101 has activity in combination with taxol and prednisone in advanced prostate cancer.

In Phase I and Phase II trials, AT-101 has demonstrated single-agent cytoreductive activity in several cancers, including chronic lymphocytic leukemia (CLL), non-Hodgkins lymphoma (NHL), and prostate cancer. Phase II combination trials were conducted in several cancers, including hormone-refractory prostate cancer and non-small cell lung cancer (with Taxotere® [docetaxel]), B-cell malignancies (with Rituxan® [rituximab]), small cell lung cancer (with Hycamtin® [topotecan]), glioma (with Temodar® [temozolomide], +/- radiotherapy) and esophageal cancer (with docetaxel, 5-fluorouracil and radiotherapy).

# Gossypol: Summary

- This is a fairly low toxicity and inexpensive natural derivative that can be used in combination with chemotherapy or other anti-apoptotic agents for a wide-range of cancers but appear especially promising for prostate, breast and B-cell hematologic malignancies. The main concern here is side-effects which include fatigue, nausea/vomitting, diarrhea, and ileus.

# Dipyridamole (Persantine)

- Anti-platelet agent, phosphodiesterase inhibitor, inhibits adenosine uptake by platelets and endothelial cells. Used as anti-thrombotic, with or without aspirin, to prevent recurrent strokes and heart attacks. Works as anti-platelet aggregation agent. It has long been researched against cancer, and is actually listed on NCI's website as an agent which enhances chemotherapy cytotoxicity against cancer.

# Dipyridamole

- a number of very small trials examining the potential usefulness of dipyridamole to enhance chemotherapeutic efficacy in sarcoma, colorectal, breast, renal cell, and prostate cancers failed to show meaningful improvement in response.

# Dipyridamole-summary

- Given the safety and low cost of dipyridamole, consider it as part of a cocktailed approach to cancers, especially melanoma and pancreas cancer. For such cancers, it is reasonable to consider dipyridamole as a secondary preventative to minimize metastases and optimize survival as well. Also, given the negative prognostic implications of elevated platelets during ca Rx, consider it in this setting as well

# Statins

- As a class, statins have diverse biological effects including improving endothelial function, stabilizing atherosclerotic plaques, attenuating oxidative stress and inflammation, immuno-modulation, as well as inhibiting the thrombogenic response. Many of these actions are executed via modulation or inhibition of post-translational protein prenylation/isoprenylation.
- immunomodulatory, antiangiogenic and anti-inflammatory effects of statins all contribute to anti-cancer potential

# Statins

- In the early 2000s, there was actually a concern that statin use may be associated with an increased risk of cancer, but analyses of several large statin studies in cardiovascular diseases dispelled the concern. Human studies can be generally divided into the use of statins as a chemopreventive to prevent cancer or as an adjuvant to treat actual cancer. While a lot of effort in terms of direct studies and meta-analyses have been devoted to finding a correlation of statin use and cancer incidences, and while risk reductions of 48% – 90% were found for breast, colon and prostate cancers in retrospective case-control studies, these are by no means a final reliable statistic.

# Statins-Prostate ca risk reduction

- By 2008 four large prospective studies (e.g. the California Men's Health Study) observed similar reductions in the risk of advanced prostate cancer, although there was no reduction in the risk of overall prostate cancer.
- Meta-analysis of 19 studies [6 randomized clinical trials (RCTs), 6 cohort and 7 case-control studies] found that while long-term statin use did not seem to contribute to a reduced incidence of prostate cancer, statins did seem to confer a protective effect in advanced prostate cancer (RR = 0.77, 95% CI: 0.64-0.93) (Int J Cancer. 2008 Aug 15;123(4):899-904).
- Retrospective report on 23,320 patients in the Finnish prostate cancer screening trial found lower prostate cancer incidence in statin users (Int J Cancer. 2010 Jan 13)

# Statins-prostate ca: synergy with radiotherapy?

- A study examining statin use in nearly 1000 patients with localized prostate cancer treated with brachytherapy found patients on statins to have lower PSAs and % positive biopsies than controls (Urol Nurs. 2006 Aug;26(4):298-303).
- Zelefsky et al reported from Memorial Sloan-Kettering Cancer Center that high risk prostate cancer patients who have undergone radiotherapy had an improved PSA-relapse free survival and concluded:
  - “data suggest that statins have anticancer activity and possibly provide radiosensitization when used in conjunction with radiotherapy in the treatment of prostate cancer” (Int J Radiat Oncol Biol Phys. 2010 May 6).

# Statins-prostate ca-secondary prevention

- Jul 15th 2010 issue of *Cancer*, data from Duke by Stephen Freedland's team showed that in a series of 1300+ men who had prostatectomy for prostate cancer, there is a 30% lower chance of recurrence for those patients who took statins. Intriguingly, men who took the highest doses saw their recurrence risk drop 50%.

# Statins-potential synergy with anti-cancer agents

- Statins may influence the efficacy of many other anti-cancer or potential anti-cancer agents, either via biological synergism or by affecting the blood levels of some agents. Although most of the studies represent *in vitro* work, such insights set a potential foundation for rational planning of a cocktailed approach against cancer. Some representative research illustrating statin synergy potentials are as follows:

# Statins-potential synergy with anti-cancer agents (cont'd)

- - potentiates sorafenib (Nexavar) cytotoxicity (Cancer Lett. 2010 Feb 1;288(1):57-67)
- - synergizes with , the cox-2 (Celebrex) inhibitor, against colon cancer (Int J Oncol. 2009 Nov;35(5):1037-43; also Int J Cancer. 2010 Feb 15;126(4):852-63)
- - synergizes with sulindac (NSAID) against colon cancer (Gastroenterology. 1999 Oct;117(4):838-47)
- - synergizes with gamma tocotrienols against breast cancer (Exp Biol Med (Maywood). 2009 Jun;234(6):639-50)

# Statins-potential synergy with anti-cancer agents (cont'd)

- - enhances the all-trans retinoic acid (ATRA)-dependent antileukemic response in acute promyelocytic leukemia (Mol Cancer Ther. 2009 Mar;8(3):615-25)
- - synergistic inhibition of lung tumorigenesis with green tea polyphenols (Clin Cancer Res. 2008 Aug 1;14(15):4981-8)
- - potentiation of the effects of lenalidomide against myeloma (Leuk Res. 2009 Jan;33(1):100-8), and thalidomide as well (Eur J Clin Pharmacol. 2006 Apr;62(4):325-9)

# Statins-potential synergy with anti-cancer agents (cont'd)

- - synergistic with an m-TOR inhibitor against acute leukemia (Anticancer Drugs. 2008 Aug;19(7):705-12)
- - enhances the cytotoxic and apoptotic effects of doxorubicin chemotherapy against human colon cancer cells and in murine tumor models (Oncol Rep. 2008 May;19(5):1205-11)
- - enhances the anti-proliferative effects of gemcitabine chemotherapy against pancreas cancer in vitro (Br J Cancer. 2005 Aug 8;93(3):319-30)

# Statins-potential synergy with anti-cancer agents (cont'd)

- - synergism with paclitaxel (Taxol) chemotherapy in K52 and HL60 cell lines (Mol Cancer Ther. 2001 Dec;1(2):141-9)
- - potentiates cisplatinum against MmB16 melanoma in rodent model (Gastroenterology. 1999 Oct;117(4):838-47)
- - potentiation anti-tumor effects of pamidronate (bisphosphonate) in vitro and in vivo (Int J Oncol. 2007 Jun;30(6):1413-25)

# Statins-potential synergy with anti-cancer agents (cont'd)

- - synergizes with zoledronic acid (Zometa, a bisphosphonate) against myeloma (Anticancer Drugs. 2006 Jul;17(6):621-9)
- - enhances trastuzumab (Herceptin) in breast cancer cell lines (Breast Cancer Res Treat. 2007 Jul;104(1):93-101)
- - potentiates the effect of saquinavir against Daudi and Raji human lymphoma cells (Oncol Rep. 2004 Dec;12(6):1371-5)
- - synergism with tamoxifen (Cardiovasc Res. 2004 Nov 1;64(2):346-55)

# Statins-potential synergy with anti-cancer agents (cont'd)

- - synergistic effect with troglitazone (PPAR agonist) in majority of cell lines tested including DBTRG 05 MG (glioblastoma) and CL1-0 (lung) (Int J Cancer. 2006 Feb 1;118(3):773-9).
- - synergizes with HDAC inhibitors against mice Lewis lung cancer model (Int J Cancer. 2002 Feb 20;97(6):746-50); and with phenylacetate against human glioma cells (J Neurochem. 1996 Feb;66(2):710-6).
- - potentiation of photocytotoxic effect of photofrin II (Bull Acad Natl Med. 1994 Jun;178(6):1177-88)
- - synergizes with TNF alpha against MmB16 melanoma (Neoplasma. 1995;42(2):69-74)

# Statins- summary

- Notwithstanding occasional contradictory reports of statins increasing the risk of cancer, given the safety (simvastatin is available as an OTC in the U.K.) and low cost of statins, plus the wide array of studies and accumulating data showing a protective effect of statins against cancer development and recurrence, statins should be seriously considered as part of a cocktailed approach for primary and secondary cancer prevention (especially for colon, breast, lung and prostate – where the data are strongest).

# Statins-summary (cont'd)

- Statins should also be seriously considered as a cornerstone ingredient to combine synergistically with other compounds such as gamma tocotrienols, cox-2 inhibitors, bisphosphonates etc for added effects in cancer treatment. Not all statins are the same however, and some (e.g. lipophilic statins such as simvastatin) may work better against certain cancers than others (e.g. hydrophilic statins such as pravastatin). Dosage may be important as well.

# Statins-summary (cont'd)

- Unfortunately, because most of the statins have patents that are expired or near expiration, there is a lack of incentive on the part of drug companies to conduct large scale clinical trials using these agents against cancer, so it is not clear that we will gain much more useful clinical insight in the near future, but strong reasons to consider adding statins to most cancer preventative or treatment cocktails unless side-effects are an issue in an individual patient.

# What about Red Yeast Rice?

- This study was designed to determine whether RYR and LV inhibit prostate tumor growth in SCID mice. RYR significantly reduced tumor volumes of androgen-dependent and androgen-independent prostate xenograft tumors compared with animals receiving vehicle alone ( $P < 0.05$ ). Inhibition by RYR was greater than that observed with LV at the dose found in RYR, showing that other compounds in RYR contributed to the antiproliferative effect. There was a significant correlation of tumor volume to serum cholesterol ( $P < 0.001$ ). RYR decreased gene expression of androgen synthesizing enzymes (HSD3B2, AKR1C3, and SRD5A1) in both type of tumors ( $P < 0.05$ ). Clinical studies of RYR for prostate cancer prevention in the increasing population of men undergoing active surveillance should be considered. *Cancer Prev Res*; 4(4); 608–15. ©2011 AACR.

# Amino-Bisphosphonates as anti-cancer agents

- Aredia (pamidronate disodium) Zometa (zoledronic acid) Fosamax (alendronate) Actonel (risedronate) and Boniva (ibandronate)
- It was originally thought that bisphosphonates are useful in bone metastases because of the ability of these agents to inhibit bone resorption; newer understanding leads us to knowledge that these drugs are really direct anti-cancer agents as well

# Amino-bisphosphonates

- Inhibit farnesyl pyrophosphate synthase, a key enzyme in the mevalonate pathway, in turn inhibiting the prenylation of small G-proteins such as Ras, Rap1, Rho and Rab, reduces the signals they mediate, and thereby prevents the growth, adhesion/spreading, and invasion of cancer cells.

# Amino-bisphosphonates (NBPs)

- Cause direct cell cycle disruption and induce apoptosis.
- This direct apoptotic effect of NBPs such as Zometa has now been reported in breast, prostate, myeloma, leukemia, colon cancers. Moreover, NBPs also independently inhibit cancer cell invasiveness, and exert anti-angiogenic effects as well via a variety of potential mechanisms.

# NBPs-limitations of current formulations

- half-lives of the drugs are very short in the blood (no more than an hour or two), the maximum concentration achieved is also up to 100 fold less than what was demonstrated to cause cancer apoptosis (self-destruction) in the test tube experiments, although concentrations are adequate for anti-invasive effects. These drugs tend to concentrate in the bones though, which explains why they are effective for controlling cancer metastatic to the bone.
- Further potential may lie in strategies such as encapsulating the NBPs in liposomes and exploiting the NBP's synergisms with other agents.

# NBPs- synergy with other agents

- NBPs have been reported to be synergistic with various cytotoxic agents, cox-2 inhibitors, imatinib, bortezomib, rapamycin, ATRA (retinoic acid), thalidomide, histone deacetylase inhibitors (HDACs), and interferon beta on growth inhibition.
- Also have immunomodulatory properties-stimulating and expanding cytotoxic gamma-delta T lymphocytes--NBPs combined use with low dose Interleukin 2 (IL-2) to induce gamma-delta T cells as immunotherapy against a variety of cancers

# NBPs--summary

- direct anticancer can be broadened to more cancer types as primary treatment used in a combinatorial manner if the latest research on gamma-delta cell therapy is confirmed and its combined use with other potentially synergistic agents should be actively explored.
- Based on principles of molecular action, MMP inhibitors such as the tetracyclines and statins should be synergistic with NBPs as well. Baulch-Brown from Australia already demonstrated Zometa synergism with Lescol (Fluvastatin) against myeloma in vitro (Leuk. Res., 2007 Mar;31(3):341-52), and similar results were obtained with Zocor by a German group (Anticancer Drugs, 2006 Jul;17(6):621-9). BPH-715 is 200x more potent as an anti-cancer than current NBPs.
- current research seems to point to Zometa as being more powerful but it has to be administered parenterally. Ibandronate (Boniva) is worth exploring for application because it can be given orally and has a better safety profile, although less data is available

# Gamma-Delta T-cell Immunotherapy

## (amino-bisphosphonates+IL-2)

- $\gamma\delta$  T cells or “gammadelta” T cells are unique to primates and represent a minority white cell in our blood (0.5-5%); yet they play an essential role in sensing ‘danger’ by invading pathogens as they expand dramatically in many acute infections and may be a key fighter in cancer as well.

# G-D T-cell immunotherapy

- mammals have two innate immune defense systems: an *adaptive immune system* unique to vertebrates in which lymphocytes participate with recognition of peptide antigens and which can be defined by memory of the target; and a more ancient *innate immunity* which is cell based (macrophages, monocytes, NK cells, NKT cells, dendritic cells) and *which has no memory* once demobilized.
- The gammadelta cells can be thought of as unconventional T cells at the interface between and linking the two immune systems, and contribute to the elimination of infections or cancers by direct and indirect killing as well as modulation and stimulation of other immune cells (eg macrophages and NK cells) and the secretion of cytokines, notably interferon gamma and TNF-alpha.

# G-D T-cell immunotherapy

- Gammadelta cells share with alphabeta T cells certain functions such as cytokine production and potent cytotoxic (cell killing) activity but **gammadelta cells recognize different sets of antigens**, usually in a non-MHC-restricted fashion, and cancers are highly susceptible to gammadelta T-cell mediated lysis which led to the proposal that gammadelta T cells can be used for cancer immunotherapy (See Kabelitz D, *Potential of human gammadelta T lymphocytes as immunotherapy for cancer*, Int J Cancer 2004 Dec 10;112(5):727-32).
- Unlike conventional T lymphocytes which recognize peptide antigens, this “alternative” T cell’s ability to recognize tumor cell ligands not seen by conventional alphabeta T cells is one property that makes them intriguing. The other unique property is the way they recognize antigens circumvents the ability to of cancer cells to eventually elude detection.

# G-D T-cell immunotherapy

- most epithelial tumors (including melanomas, pancreatic adenocarcinomas, squamous cell carcinomas of the head and neck, and lung carcinoma – See *Scan J Immunol*, 2007;66(2-3):320-8) were susceptible to allogeneic gammadelta T-cell lysis and in the case of an established ovarian carcinoma, to autologous gammadelta T-cell killing
- efficient killing of cancer stem cells by gammadelta T cells (Todaro M, et al. *J Immunol*. 2009 Jun 1;182(11):7287-96).

# G-D T-cell immunotherapy

- Pioneering work by the Italian team Casetti et al. elegantly demonstrated that co-stimulation simply with interleukin 2 plus amino-bisphosphonates induced up to 100-fold increases in the numbers of peripheral blood V $\gamma$ 9V $\delta$ 2 T cells in animals.
- Together with a German team led by Wilhelm et al. this laid the ground work for subsequent clinical endeavors in this field (Casetti R et al. Drug-Induced Expansion and Differentiation of V $\gamma$ 9V $\delta$ 2 T Cells In Vivo: The Role of Exogenous IL-2, J Immunol 2005;175(3):1593-8).

# G-D T-cell immunotherapy

- Italian team led by Dieli F of Palermo initiated a phase I clinical trial in metastatic hormone-refractory prostate cancer to examine the feasibility of using zoledronate in combination with low-dose interleukin 2 (IL-2) to stimulate gammadelta cells against the cancer and registered 3 partial remissions and five stable diseases out of nine patients (Dieli et al. Cancer Res.2007;67(15):7450-7) .

# Artemisinin and its analogues

- Artemisinin or Qinghaosu, derived from the leafy portions of the sweet wormwood plant *Artemisia annua* L. or qinghao, and isolated in 1972 by Chinese chemists, is a potent anti-malarial that has revolutionized modern malaria treatment, and led to derivative drugs including artesunate (water soluble), and artemether (lipid soluble, crosses BBB the best), among others
- artemisinins exhibit potent anticancer effects in a variety of human cancers (Expert Rev Mol Med. 2009 Oct 30;11:e32), a fact which has been known for almost three decades but relatively unexplored.

# Artemisininins

- One of the most notable semi-synthetic derivative drug from artemisin is artesunate (ART), which was developed for malaria in the 1980's was noted to have anti-cancer activity along with other artemisininins by the early 1990's (J Nat Prod. 1993 Jun;56(6):849-56), with Lai and Singh reporting that artemisinin selectively killed MOLT-4 lymphoblastoid leukemia cells in 1995 (Cancer Lett 1995; 91:41-46).

# Artemisininins

- Subsequent research by Thomas Efferth's team in Germany demonstrated artesunate's in vitro efficacy against multiple tumor lines (Int J Oncol. 2001, 1:767-773) and was most active in vitro against leukemia and colon cancer while modestly effective against melanomas, breast cancer, ovarian cancer, prostate cancer, glioma, and renal cancer.
- The same research team was also responsible for elucidating much of the molecular mechanisms of efficacy of ART against cancer, which included direct cytotoxicity, anti-angiogenesis as well as induction of apoptosis (Drug Resist Updat. 2005 Feb-Apr;8(1-2):85-97).

# Artemisininins

- Anecdotally, dogs with bone cancer and lymphosarcoma have been reported to rapidly respond to artemisinin, and patients with prostate cancer, brain tumors, pancreas cancer, breast cancer were also anecdotally reported to have been helped by artemisin derivatives.
- Reportedly, Dr. N. Singh from the U. of Washington mentioned the case of a man (in India) with brain cancer who had been in coma for 5 months who came out of the coma after 21 days of IM injections of artemether.

# Artemisininins-summary

- Despite some concern for neurotoxicity based on animal studies, ART and related compounds are some of the least toxic medications on the market for any condition, without clinically relevant toxicity after extensive oral and parenteral use in various populations for the past two decades, except for sporadic and transient cardiac dysrhythmias. These compounds are also relatively inexpensive, being dispensed mainly in the third world in poor populations where malaria is endemic. With the demonstrated bioactivity in the laboratory and the promising anecdotal cases, these seem to be reasonable compounds to try against cancers , either in combination or when other treatments fail.

# Ursodeoxycholic acid (Actigall, URSO) for chemoprevention

- Ursodiol or Ursodeoxycholic (Actigall, URSO) is a naturally derived bile acid that decreases the amount of cholesterol produced by the liver and absorbed by the intestines. Interestingly, ursodiol is found in large quantities and the major therapeutic ingredient in bear bile, which is an established if controversial member of traditional Chinese medicine's pharmacopoeia.
- Ursodiol helps break down cholesterol that has formed into stones in the gallbladder and is also hepatoprotective. Ursodiol also increases bile flow, which is why it is useful in cholestatic conditions such as biliary cirrhosis. Since the 1980's, Urso has been in widespread clinical use for biliary conditions.

# URSO

- Earnest DL et al. from the U. of Arizona reported as early as 1994 that Urso is a potential chemopreventive agent in experimental colon cancer and highlighted a role of bile salts in modulating gastrointestinal cancer development.
- It wasn't long before Urso became a recognized chemopreventative agent against colon cancer in those with inflammatory bowel disease (See Itzkowitz SH, Gastroenterol Clin North Am. 2002 Dec;31(4):1133-44).

# URSO

- In 1997, the Korean team Park YH et al. reported that Urso induced apoptosis (suicide) of liver cancer cells in vitro (Arch Pharm Res. 1997 Feb;20(1):29-33) and the same team further demonstrated derivatives of Urso had efficacy against prostate and breast cancer cell lines in later studies.
- Im and Martinez demonstrated that Urso induced apoptosis in colon cancer partly via modulation of EGFR/Raf-1/ERK signaling (Nutr Cancer. 2005;51(1):110-6.)

# URSO

- Clinical data for Urso as a cancer treatment is not available and its main potential seems to be as a chemoprevention strategy in those at high risk for colon or liver cancers , but attempts to synthesize Urso and other bile salt derivatives for cancer treatment is in progress.

# Off Label Pharmaceuticals for Cancer Cont'd...

Agent	Therapeutic  Daily Dose
ITRACONAZOLE	200 mg. (anti-angiogenic) NSCLC & Prostate
MANUMYCIN	5-10 mg. (FARNESYLTRANSFERASE & PARP-1 INHIBITOR, ALSO INHIBITS RAS, IL-1, HIF-1A, &TELOMERASE) MULTIPLE CANCERS

# Celebrex (COX-2 inhibitor)

- Celebrex (celecoxib), is a promising chemopreventive [Arber et al.: N Engl J Med 2006;355:885-895](#); [Bertagnolli et al.: N Engl J Med 2006;355:873-895](#)
- Besides down-regulating COX-2, celebrex selectively affects genes & pathways involved in inflammation and malignant transformation in tumors. [Digestion 84 \(3\), 169-184 \(May 2011\)](#)
- Botanical and Nutritional co-administration can significantly improve response. Curcumin, ginger, boswellia, andrographis, Chinese Skullcap, bromelain, addition of B-6, Magnesium, and Zinc as well.
- Celebrex often effective for cancer-related pain relief, especially for bone metastases.
- DOSE: 100-200 mg. 2x daily, which can be taken with Cimetidine 200-400 mg.)-Don't use in sulfa allergic pts!

# Celebrex (COX-2 inhibitor)

- Anti-prostate cancer effects. *Drug Chem Toxicol.* 2011 Dec 14.
- Regression of Prostate Tumors upon Combination of Hormone Ablation Therapy and Celecoxib in vivo. *Prostate.* 2011 June 1; 71(8): 813–823. doi:10.1002/pros.21297.
- EGCG (Green tea) synergistic with celebrex against pancreatic cancer. *European Journal of Pharmacology* 684 (2012) 36–43
- Curcumin and Celebrex Synergistically Inhibits the Growth of Colorectal Cancer. *Clinical Cancer Research* Vol. 11, 6738-6744, September 15, 2005
- **Rapamycin and celebrex synergist against** metastasized malignant melanoma. *Oncol Rep.* 2008 Feb;19(2):547-53.

# Celebrex (continued)

- DHA-rich fish oil with celebrex modulates HSP70 and p53 proteins in prostate cancer. *Int J Cancer*. 2006 Oct 1;119(7):1586-98
- Cox-2 inhibition also potentiates the effects of chemotherapy *Mol Pharmacol*. 2009 Jun;75(6):1364-73. Epub 2009 Mar 5.
- In liver cancer the combination of celebrex with chemotherapy killed more cancer cells together than chemo alone. *Cancer Prevention Research*, 2011; DOI: [10.1158/1940-6207.CAPR-10-0317](https://doi.org/10.1158/1940-6207.CAPR-10-0317)
- In Multiple myeloma (MM), celebrex can reduce drug-resistance-- this effect is achieved via the blockage of multiple targets that are critical for MM cell growth and survival. *Blood*. 2005;106:4330-4338

# Celebrex

- **Synergist with Herceptin & EGFR Targeting Drugs**  
Mediates antitumor effects through the inhibition of PI-3/Akt signaling independently of COX-2. *Mol Pharmacol.* 2006 Nov;70(5):1534-41. Epub 2006 Aug 3.
- Enhances the anti-cancer effects of xeloda while reducing side effects (esp hand-foot syndrome). *J Cancer Res Clin Oncol.* 2010 Nov 27.
- Curcumin and celebrex synergistically inhibit cancer. *Digestion.* 2006;74(3-4):140-4. Epub 2007 Jan 15.
- N-3 fatty acids (EPA/DHA) are also synergistic with celebrex (*Nutr Cancer.* 2007;59(1):14-20. *J Periodontol.* 2008 Oct;79(10):1934-4)

# Noscapine (Opium alkaloid)

- Commonly used antitussive agent available in Europe, Asia, and South America.
- A tubulin-binding agent, increases the time that cellular microtubules spend idle in a paused state
- Inhibits Bcl-2 expression
- Crosses the blood-brain barrier



# Noscapine

- Noscapine was able to inhibit cancer at doses which produced little or no toxicity, including no adverse effects on the primary immune response (Ke Y et al. Cancer Immunol Immunother. 2000 Jul;49(4-5):217-25). More recently, Newcomb et al. from New York also demonstrated potential anti-angiogenic activity of Noscapine as an alternate anti-cancer mechanism (Int J Oncol. 2006 May;28(5):1121-30)

# Noscapine

- Noscapine was shown to inhibit progression and metastases (60% and 65% respectively) in PC3 human prostate cancer-bearing immunodeficient mice  
Anticancer Res. 2008 Nov-Dec;28(6A):3701-4.)

# Noscapine-summary

- Potentially useful against CLL leukemia/lymphoma/myeloma, prostate cancer, non-small cell lung cancer, glioma (administered alone or in combination with chemo and/or radiation to enhance cytotoxicity), hormone resistant breast cancer, or perhaps co-administered with taxanes.
- Distinct advantages include i) oral bioavailability, ii) encouraging experimental data, iii) low toxicity, iv) low cost, and v) synergistic potential with other modalities and drugs.