

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

A4M Integrative Cancer Therapies

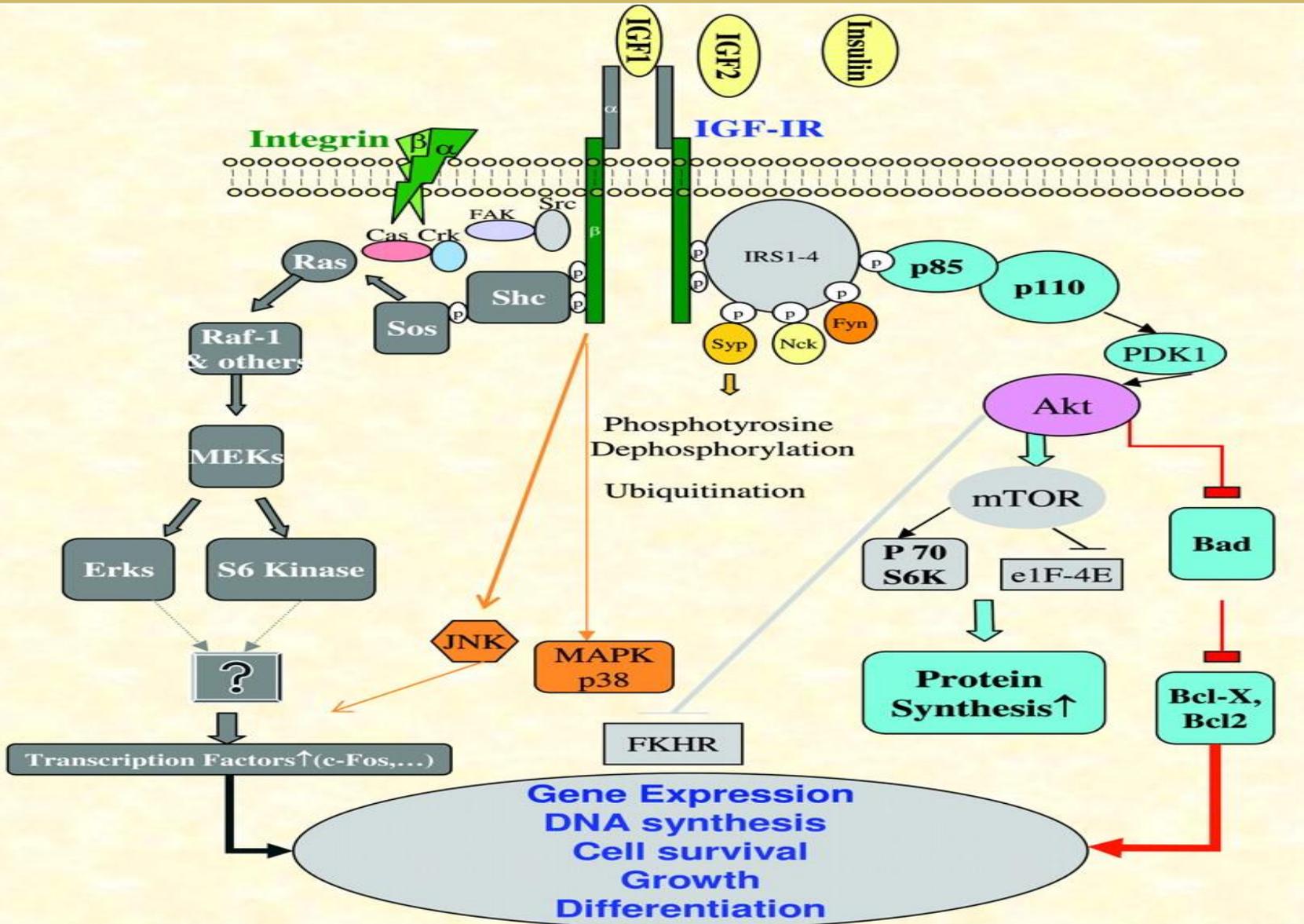
Module 6

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.

# 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 Vgamma9Vdelta2 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 9V 2 T Cells In Vivo: The Role of Exogenous IL-2, J Immunol 2005;175(3):1593-8).

# G-D T-cell immunotherapy

- In 2005, Bennouna et al. presented a phase I trial of 18 BrHPP (Phosphostim) and low dose IL-2 treated patients with solid tumors in a poster session at ASCO (JCO, 2005; 2005 ASCO Annual Meeting Proc 23(16S), Pt II of II:2536).

# G-D-T-cell immunotherapy

- *British Journal of Cancer* (2011) **105**, 778–786.  
doi:10.1038/bjc.2011.293
- **Background:**
- Adoptive transfer of *ex vivo* expanded autologous V $\gamma$ 9V $\delta$ 2 T cells may be of therapeutic benefit for cancer because of their potent direct cytotoxicity towards tumour cells, synergistic cytotoxicity when combined with aminobisphosphonates and enhancement of antibody-dependent cell-mediated cytotoxicity.

# G-D-T-cell immunotherapy

- **Methods:**
- To determine the feasibility and clinical safety of therapy with *ex vivo* expanded, activated V $\gamma$ 9V $\delta$ 2 T cells in combination with zoledronate, we enrolled 18 subjects with advanced solid tumours into a phase I clinical study. Administered indium<sup>111</sup>-oxine-labelled V $\gamma$ 9V $\delta$ 2 T cells were tracked in a cohort of patients.

# G-D-T-cell immunotherapy

- **Results:**
- Administered  $V\gamma 9V\delta 2$  T cells had an activated effector memory phenotype, expressed chemokine receptors predictive of homing to peripheral tissues and were cytotoxic *in vitro* against tumour targets. Adoptively transferred  $V\gamma 9V\delta 2$  T cells trafficked predominantly to the lungs, liver and spleen and, in some patients, to metastatic tumour sites outside these organs. No dose-limiting toxicity was observed, but most patients progressed on study therapy. However, three patients administered  $V\gamma 9V\delta 2$  T cells while continuing previously ineffective therapy had disease responses, suggesting an additive effect.

# G-D-T-cell immunotherapy

- **Conclusion:**
- Therapy with aminobisphosphonate-activated  $V\gamma 9V\delta 2$  T cells is feasible and well tolerated, but therapeutic benefits appear only likely when used in combination with other therapies.

# 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-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.

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

Agent	Therapeutic Daily Dose
<b>Hydroxychloroquine</b>	400-800 mg. (<CXCR4)
LMW Heparin	(anti-thrombotic/anti-angiogenic)
Baclofen	5 mg. bid (>GABA, antagonist to $\beta$ -adrenergic cascade) Liver/pancreatic/breast cancer
Naltrexone (Low-dose)	1.5 to 4.5 mg at bedtime (opioid antagonist, upregulated the expression of the opioid growth factor & its receptor) Ovarian cancer
3-Bromopyruvic Acid and sodium dichloroacetate	Inhibits Glycolysis

# Tetrathiomolybdate

- In cancer patients has shown to reduce the serum levels of Interleukin (IL)-6, IL-8, vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF)  
<http://clincancerres.aacrjournals.org/content/9/5/1666.log>
- TM lowering of Cp also inhibits NFκ-B. Lowering Cp to low normal range during chemotherapy can improve chemosensitivity. TM increases platinum uptake by ovarian cancer cells.
- Lowering Cp <15 after obtaining CR and maintaining for 3 years induces angiogenic blockade, and subsequent tumor (and tumor stem cell) dormancy of some sort.

# 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

## *In Vitro*

- Noscapine inhibits paclitaxel resistant ovarian cancer cells (Zhou, J et al. J Biol Chem. 2002 Oct 18;277(42):39777-85); C6 rat glioma when administered alone, (as well as augmented the cytotoxicity of radiation and chemotherapy upon C6 rat glioma cells when administered concomitantly – Surg Neurol. 2006 May;65(5):478-84), HL60 and K562 myelogenous leukemic cells Anticancer Drugs. 2007 Nov;18(10):1139-47),

# 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.