LEARNING OBJECTIVES - AT THE END OF THIS MODULE, PARTICIPANT WILL BE ABLE TO:

1. Speak knowledgeably about the number of insulin and IGF receptors on breast cancer cells
2. Understand and name modes of cellular secretion
3. Name the three “effects” of IPT + chemotherapy
WE WILL REVIEW SOME MECHANISMS BEHIND IPT/IPTLD/FCBRM
WE WILL REVIEW SOME HISTORY
WE WILL REVIEW SOME RESEARCH LITERATURE
The secretion of insulin and IGF-1, and the elaboration of specific receptors for these ligands, has been well characterized in human breast cancer cell lines.


Human breast cancer cells have six times more insulin receptors (1) and ten times more IGF-I receptors (2) than normal tissues in the body.


Of all of the known growth factors, IGF-I has been reported to be the most potent growth-promoting mitogen for breast cancer cells.

Supraphysiologic concentrations of insulin can replace the IGF-I requirement in defined media through cross-reaction with the IGF-I receptor.

Some “new” terminology…

Modes of Cellular Secretion

- **Endocrine**
- **Exocrine**
- **Paracrine**
- **Autocrine**
The combination of insulin and IGF-I operates autonomously at the cellular level within tumors, and this operation is free from any higher level of integrated control…

(Cont’d)…
The two work together in an autocrine and/or paracrine manner and in a complementary fashion, with IGF-I being the major anabolic hormone responsible for mediating messages about growth in the tumor, while insulin regulates and provides the fuel for these processes.

Insulin receptors are widely distributed in mammalian organisms with their being from 100 to 100,000 receptors per cell in different tissues. Rarely are there any cells having no receptors at all.

Supraphysiologic concentrations of insulin can replace the IGF-I requirement in defined media through cross-reaction with the IGF-I receptor.

And two more pieces of evidence...
Insulin enhanced the cytotoxic effect of methotrexate in MCF-7 human breast cancer cells in vitro by a factor of up to ten thousand.

Preincubation of MDA-MB-231 human breast cancer cells in vitro with insulin resulted in an increased intracellular accumulation of ellipticine with a concomitant increase in cytotoxicity.

Miracles do not happen in contradiction to nature, but in contradiction to that which is known to us of nature.

Saint Augustine
How does it work?

How could this be?
Increased Intracellular Dose Intensity

MEMBRANE EFFECTS
- Altered Cell Membrane Permeability
- Increased Intracellular Dose Intensity

Exogenous Insulin

Low-Dose Chemo

IGF Receptors

Insulin Receptors

METABOLIC EFFECTS
- Increased S-Phase Sensitivity to Anticancer Drugs

Schema of IPT Mechanisms

Ligand effect is a function of receptor concentration
The Benefits of Chemotherapy

Chemotherapy drugs are powerful, effective, cell-killing agents.
Problem Areas in Cancer Chemotherapy

1) - An adequate **intracellular dose intensity** requires the systemic administration of **high doses** of drugs

2) - **Lack of tissue specificity** for drugs

1) + 2) = Widespread dose-related drug side effects
All great discoveries are made by those whose feelings run ahead of their thinking.

C.H. Parkhurst
What would be the elements of an ideal solution to this cancer/chemotherapy dilemma?

• 1) To develop a method of differentiating the cancer cell population from the normal cell population.

• 2) To deliver lowered doses of drug more specifically into this differentiated cancer cell population.

• 3) To maintain and/or enhance chemotherapy’s cell-killing effectiveness in cancer cells.

• 4) To reduce or avoid chemotherapy side effects in normal cells.
IPT & Cancer Chemotherapy

I - Cellular Differentiation Effect

II - Membrane Effect

III - Metabolic Effect
IPT & Cancer Chemotherapy - I

I - Cellular Differentiation Effect

- Excess of IR & IGF-R on cancer cells membranes differentiates these cell populations from a host normal cells. Insulin allows us to take advantage of this cellular physiology.

- Chemotherapy can act as a “smartbomb”.

- Relative sparing of host normal tissues from harmful drug side effects.
Ligand effect is a function of receptor concentration

Normal Somatic Cells

Malignant Cells

Relative IR & IGF-R Concentrations

IR
IGF-R
IR
IGF-R

6X
10X
II - Membrane Effect

- Increased cell membrane permeability
- Increased intracellular dose intensity
- Lowered total dose of drugs
- Reduced dose-related side effects
- Shorten treatment cycle intervals
Mechanisms of Membrane Effects

1) **Insulin activation of delta-9 desaturase**

- **Stearic acid** - saturated - 
  - m.p. 68 deg. C

- **Oleic acid** - monounsaturated - 
  - m.p. 5 deg. C

At 37 deg. C

*Membrane fluidity/permeability*
Mechanisms of Membrane Effects (cont’d)

2) Drug adsorption with glucose molecules with transmembrane transport then occurring via the insulin-activated glucose transport protein (i.e., GLUT 4)

3) Adsorption of drug molecules onto insulin with the resulting chimeric drug-insulin complex being internalized into the cell by a process of receptor-mediated endocytosis
Schema of IPT Mechanisms

Exogenous Insulin

Low-Dose Chemo

Insulin Receptors

IGF Receptors

MEMBRANE EFFECTS
- Altered Cell Membrane Permeability
- Increased Intracellular Dose Intensity

x 6

Synergy

x 10

METABOLIC EFFECTS
- Increased S-Phase
- Increased Sensitivity to Anticancer Drugs
IPT & Cancer Chemotherapy - III

III - Metabolic Effect

- Increased S-phase fraction
- Potentiation of cell-cycle phase-specific anticancer drugs
- Increase in proportion of cancer cells killed per chemotherapy cycle
Drugs are most effective in cycling populations of cells.. and.. hormonal manipulations directed towards regulating cell growth, rather than producing cell death, combined with chemotherapy should be more effective in increasing cure rates in mammary carcinomas.

In vitro, after adding insulin to an asynchronous population of breast cancer cells, the S phase fraction was 66% compared to only 37% in the controls.

Supraphysiologic concentrations of insulin can replace the IGF-I requirement in defined media through cross-reaction with the IGF-I receptor.

Schema of IPT Mechanisms

- Altered Cell Membrane Permeability
- Increased Intracellular Dose Intensity

Exogenous Insulin

Low-Dose Chemo

MEMBRANE EFFECTS

- Increased Sensitivity to Anticancer Drugs
- Increased S-Phase

METABOLIC EFFECTS

- Increased Sensitivity to Anticancer Drugs
IPT & Cancer Chemotherapy

• “Smart Bomb” effect:
  Excess of insulin-sensitive receptors on human cancer cells causes predominance of insulin effect in cancer cells, sparing normal host tissues = INCREASED SAFETY

• Synergy of insulin’s membrane and metabolic effects enhances anticancer drug action in cancer cells = INCREASED EFFICACY
Insulin Potentiation Therapy (IPT)

• IPT is a chemotherapy-based protocol using insulin as a biologic response modifier of the endogenous mechanisms of malignancy.

• In IPT, insulin is used to selectively target cancer cells with lowered doses of chemotherapy drugs, enhancing drug effects on these cells and, at the same time, effectively reducing dose-related chemotherapy side effects on host normal tissues.
Canadian Frederick Grant Banting, MD, discovered insulin in 1921.

He received a Nobel Prize in 1923.

Diabetes had suddenly become a curable disease.
IPT HISTORY

Donato Perez Garcia, M.D. (1886-1971)
A surgeon lieutenant in the Mexican military.

He theorized that insulin would enhance tissue assimilation (drug uptake) better intra-cellularly, and perhaps in smaller doses.
IPT HISTORY

Dr. Perez Garcia’s preliminary work with insulin involved an innovative course of self-treatment for an emaciating gastrointestinal problem he had suffered from for years. All previous treatments had failed to resolve it.

The use of insulin was successful. His symptoms disappeared and his weight became normal.
IPT HISTORY

Dr. Perez Garcia developed the use of insulin as a biological modifier during the 1930s and 1940s for the treatment of human disease.
1930s – First patient with tertiary neurosyphilis successfully treated using low dose Salvarsan, an aresenic based anti syphilitic developed in Germany by Dr. Paul Ehrlich, with insulin. Dr. Perez Garcia reasoned that treatment might be improved with the addition of insulin to help the brain assimilate the anti-syphilis medications.

An animal study using this concept showed an increased brain uptake of Salvarsan – and this data was published in Revista Medica Militar (1938).
1930s – Antibiotics had not yet been discovered.

Using extremely toxic heavy metal drugs – mercury and arsenic salts – doctors could often successfully treat the disease in its early stages.

When syphilis reached its final or tertiary stage, entering the central nervous system (CNS), there was little the doctors could do.
1946 – IPT first used to treat cancer. Patient treated using low dose chemotherapy survived and lived disease free for another 30 years.

Documented by Dr. Donato 1 & 2
1937 – Dr. Perez Garcia was invited to the United States to demonstrate his therapy at the Austin State Hospital in Austin, Texas, and at St. Elizabeth’s Hospital in Washington, D.C.

1944 – Invited to treat patients at the San Diego Naval Hospital, producing the same positive results in patients with neurosyphilis, malaria, rheumatic fever, and cholecystitis.

This led to a TIME Magazine write-up of Dr. Perez Garcia and his insulin therapy.
2nd and 3rd Generations have followed in his footsteps:

His son, Donato Perez Garcia Bellon, (1930-2000) and grandson, Donato Perez Garcia, III (1958-present)
IPT HISTORY

• 1977: Presentation on IPT made at the National Institutes of Health, Office of Alternative Medicine, POMES conference in August 1997 by Dr. Perez Garcia and Dr. Steven Ayre.

• 2000: A Best Case Series presentation made to the members of the Cancer Advisory Panel of the Center for Complementary and Alternative Medicine at the National Institutes of Health in Bethesda, Maryland.

http://contemporarymedicine.net/?page_id=568
“Overview

Despite individual reports, there are no published scientific studies available showing that IPT is safe or effective in treating cancer in humans. IPT may have serious side effects.”

http://www.cancer.org/treatment/treatmentsandsideeffects/complementaryandalternative medicine/pharmacologicalandbiologicaltreatment/insulin-potentiation-therapy
ARTICLES BASED ON STUDY AND CLINICAL PRACTICE:


This study was designed to examine effect of insulin on methotrexate cytotoxicity to MCF-7 cells and thereby establish the principle that appropriate metabolic manipulation can increase tumor cell sensitivity to cytotoxic drugs.
Summary:

“These [lab] data demonstrate that insulin can increase the cytotoxic effect of methotrexate up to 10,000-fold in MCF-7 cells in vitro ... It is premature to extrapolate these in vitro observations to a clinical trial, but it is possible that the 10,000-fold increase in methotrexate cytotoxicity produced by insulin may establish not only a new way to increase the therapeutic effect of methotrexate, but also the principle that metabolic modifiers should be examined as a means to increase tumoricidal effects of chemotherapeutic agents.”

First published clinical study for the application of insulin in combination with methotrexate in patients with breast cancer.
Summary:

“In this study, methotrexate at this safe low dose did not have an antitumoral effect when used alone (group 2), but it did produce a significant antitumoral effect when administered after insulin (group 1) ...  

As reported previously, our results support the hypothesis that insulin can potentiate the antitumoral effect of methotrexate and confirm in vivo previously reported in vitro results. Our results also show insulin potentiation of methotrexate in this condition, where insulin alone did not promote an increase in tumor growth (group 3) ...  

Certainly, the response to insulin is more intense in most tested cancer cells than in most normal cells. This is probably because cancer cells are richer in receptors for insulin-like growth factors that are cross-stimulated by insulin.”

Presents 3 cases which demonstrate the efficiency of IPT in the treatment of metastatic tumors, following failure of standard chemotherapy.
Summary:

“In those cases we achieved remission for 15, 21 and 8 months, respectively. The first patient was lost to follow up after June 2008 and the other two are in remission until now, receiving maintenance treatment.

Their quality of life improved rapidly after the first 2-3 courses and gave the patients the opportunity to restore their normal work activity after 2-3 months from the beginning of treatment. The third patient was additionally treated with LHRH agonist.

Treatment was very well tolerated, the only complaints being weakness and sleepiness during the first day. Lab examinations showed no significant toxicity. In our 3 patients we observed insignificant increase of liver function tests in the first 6 weeks, while these normalized without any additional measures during treatment.”

Present the results of their three-year experience applying IPT in the treatment of 196 patients with diagnosed with a variety of neoplastic diseases.
Summary:

“Laboratory tests demonstrate that the dose related toxicity of chemotherapeutics can be largely mitigated when applying them in conjunction with insulin, at a fractionated dose following a dose dense regimen ... The average number of IPT treatments received amongst patents who completed the initial six was thirteen treatments total ... Patients easily tolerated IPT ...

Only two of the one hundred forty-eight patients with initially low Hb level needed blood transfusion while in active treatment...

Upon follow-up, eighty-eight of 108 patients (81%) with advanced metastatic disease reported a subjectively significant improvement in their quality of life.”


• Damyanov Ch, Gerasimova D et al. Low-Dose Chemotherapy with Insulin (Insulin Potentiation Therapy) in Combination with Hormone Therapy for Treatment of Castration-Resistant Prostate Cancer. *ISRN Urol.* Volume 2012; Article ID 140182
IPT Documented cont.

- Maniotis A, Valyi-Nagy K. *The Rationalism of Insulin Potentiation Therapy in Cancer*. Prepared pro bono at the request of the J.W. Harvey of The Elka Best Foundation, a Project of the National Heritage Foundation.

IPT Documented cont.


IN PROCESS:

• BACF is working with the National Institute of Health/National Cancer Institute/Office of Cancer Complementary and Alternative Medicine (NIH/NCI/OCCAM) on The Best Case Series, documenting cases using IPT for Cancer.

• IPT is formally under review for studies by NCI/OCCAM, who lists it in their top 5 therapies to approve.
IPT is an off-label use of chemotherapy and other medications and insulin: off-label use of drugs is common practice throughout the world.
Insulin Potentiation Therapy

Has been an ongoing
Renaissance in
Cancer Chemotherapy
For Nearly 70 years
Many Thanks to My Teachers

• Dr. Douglas Brodie
• Dr. Frank George
• Dr. Donato III
• Dr. Steven Ayer
• Dr. Richard Linchitz
Questions?
Overview

The Contribution of Cytotoxic Chemotherapy to 5-year Survival in Adult Malignancies

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ABSTRACT:
Aims: The debate on the funding and availability of cytotoxic drugs raises questions about the contribution of curative or adjuvant cytotoxic chemotherapy to survival in adult cancer patients.
Materials and methods: We undertook a literature search for randomised clinical trials reporting a 5-year survival benefit attributable solely to cytotoxic chemotherapy in adult malignancies. The total number of newly diagnosed cancer patients for 22 major adult malignancies was determined from cancer registry data in Australia and from the Surveillance Epidemiology and End Results data in the USA for 1998. For each malignancy, the absolute number to benefit was the product of (a) the total number of persons with that malignancy, (b) the proportion or subgroup(s) of that malignancy showing a benefit, and (c) the percentage increase in 5-year survival due solely to cytotoxic chemotherapy. The overall contribution was the sum total of the absolute numbers showing a 5-year survival benefit expressed as a percentage of the total number for the 22 malignancies.
Results: The overall contribution of curative and adjuvant cytotoxic chemotherapy to 5-year survival in adults was estimated to be 2.3% in Australia and 2.1% in the USA.
Conclusion: As the 5-year relative survival rate for cancer in Australia is now over 60%, it is clear that cytotoxic chemotherapy only makes a minor contribution to cancer survival. To justify the continued funding and availability of drugs used in cytotoxic chemotherapy, a rigorous evaluation of the cost-effectiveness and impact on quality of life is urgently required. Morgan, G. et al. (2004). Clinical Oncology 16, 549–560

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Key words: Chemotherapy, combined modality treatment, palliation, quality of life, radiotherapy, survival
Change in the US Death Rates* by Cause, 1950 & 2002
(A 2005 Presentation From the American Cancer Society)

Rate Per 100,000

Heart Diseases: 1950 - 586.8, 2002 - 240.1
Cerebrovascular Diseases: 1950 - 180.7, 2002 - 56.0

* Age-adjusted to 2000 US standard population.
Sources: 1950 Mortality Data - CDC/NCHS, NVSS, Mortality Revised.

©2005, American Cancer Society, Inc.
Change in the US Death Rates* by Cause, 1950 & 2010
(A 2005 Presentation From the American Cancer Society plus
2010 Data from the CDC)

* Age-adjusted to 2010 US standard population.

Sources:
1950 Mortality Data - CDC/NCHS, NVSS, Mortality Revised.

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