Donald Yance
Immune Checkpoint Inhibitors
<u>Goal: Getting durable remissions with them</u>

Updated 8/18/22 Transcribed by Peter Brodhead CN, DHom, ETMS practitioner

Source of information for this handout - Donald Yance 2017 presentation Immune Checkpoint Inhibitors pt.1 & 2 along with his slide presentation on this topic

Vagal Nerve - a key factor that runs the parasympathetic nervous system - When the parasympathetic nervous system is activated the immune system works better. Learn how to activate it to help manage stress - *see my handout on activating the Vagal nerve response.*

Following the **Circadian Rhythm** of the day can support immunity - get morning light in the eyes get outside take off your sun glasses and get light in your eyes early in the day. Get noon day light - eat outside for lunch. Try to watch the sunset. This sets up the Circadian Rhythm for your body supporting immunity and helping you get a better and deeper sleep which really helps immunity. Exercise during the day and eliminate blue light at night turn off your electric devises 2 hours before bed or change the light settings to orange light on your phone or computer. Red light is fine for your bedroom clock if it isn't red cover it. Keep your bedroom as dark as possible and get to bed before 11pm to reset your body, brain and immune system.

Moving the Lymph is very important when the body is breaking down a cancer. Herb Pharm's Herbal Detox is the original Hoxey Formula and is a great support for moving the lymph. Get the lymph moving to help the body eliminate toxins. Gentle exercise such as brisk walking and or biking. Use a rebounder which is a small trampoline to help the lymph move.

Understanding the Immune System: There are 2 components of the immune system

1. **Innate Immunity** - non specific immunity - this is the immune system we are born with - the first line of defense that is activated to go after bacteria, viruses and pathogens.
2. **Adaptive Immunity** or learned immunity this consists of bone marrow derived B-cells. B cells recognize specific antigens such as: Chicken pox. Vaccines by pass the Innate Immune system and activate the adaptive immune system.

Cancer - starts from a less inflammatory and as it grows and spreads progresses to a pro-inflammatory state. Checkpoint inhibitors work best in this pro-inflammatory state.
Low grade cancers do not respond well to checkpoint inhibitors. High grade cancers do respond. Cancer grows during the day under stress hormones. BiPhasic way tumors grow by a different pathway at night.
KRAS mutations in the cancer are good indicators for a response with checkpoint inhibitors.

Lymphocytes:
T-Cells (originally derived from the Thymus Gland but are also made all over the body)
CD8 + T cells are what Checkpoint inhibitor drugs activate. Your Cytotoxic T-Cells have to be armed and ready to allow the Checkpoint Inhibitors to work properly.
CD4+ cells suppress and buffer - CD4 T helper cells

Dendrenic Cells:
Are antigen-presenting cells - Tumor antigens are taken up by antigen-presenting cells.
TH1 Helper cells are critical for successful immunity against cancer.
DHEA levels support TH 1

TH2 works the opposite and helps the cancer grow. High Cortisol levels (ie. Stress) helps TH2 (*think of DHEA as cool and Cortisol as hot - cancer as it grows gets hotter ie. It is more Inflammatory)*
Regulatory T-Cells are called TREGS can help prevent auto-immunity but in cancer TREG cell can be used to prevent the immune system from recognizing that cancer is there. (Like a bodyguard to protect the cancer from the immune system).
There are many components of the immune system that get hijacked and become a support for the growth of cancer.
Botanical medicine can down regulate TREG cells. TAMS (tumor associated macrophages) are another one.
Neutrophils - N1's are important to fight infection. N2's collaborate with cancer.
To summarize TH2 and N2's are bad. TREG cells are bad also.

Understanding Cancer genes and cancer growth pathways

p53 - gene is the guardian of the genome and protects against cancer forming. Do everything you can to protect this and keep it "wild type" ie. Healthy and normal. Loss of p.53 pathway can contribute to a more aggressive tumor behavior and also resistance to cancer therapies. The typical "Standard American Diet" turns off the p.53 gene. High sugar (high glycemic diet) - refined sugars and starches - white flour, white rice, white sugar, high fructose corn syrup sweetened beverages, red meat - from commercial feed lot not grass fed organic, fast foods - fried in bad oils are major examples of foods that turn off the p.53 gene. Eat only authentic real unprocessed food and stay away from packaged food. Eat organic foods whenever possible - go to the **www.ewg.org** The environmental working group and get the list of the dirty dozen (worst pesticide laden fruits and vegetables) and the clean 15 (the least sprayed fruits and vegetables). These foods and supplements turn on the p.53 gene: Melatonin, Curcumin, Resveratrol, Quercetin, Ginseng, Vitamin A, Flavonoid rich foods including apigenein - parsley is a rich source of this, fermented soy, green tea, milk thistle, Vitamin D3,
Two other important genes that you want to "up regulate" are the **p.21 & p.27** genes they inhibit the formation of cancer. Turmeric (Curcumin) up regulates these. Green Tea, Broccoli compounds isothiocyanates and sulforaphane up regulate these. IP-6 (Inositol hexaphosphate) helps this. Grape seed extract, Tocotrienols (a form of Vitamin E). Feverfew (Parthenolide), American Ginseng (Panax Quinquefolius), Chaga Mushroom, Salvia miltiorrhiza (Chinese red sage), Artemissinin, Chinese skullcap (Baicalensis), Bitter Melon are all some of the botanicals, foods and vitamins that up regulate the p.21 and p.27 genes.

One of the best ways to see how a person with cancer is doing is to read a **CBC blood test report.** When cancer is progressing - Lymphocytes go down and Neutrophils go up. You don't want to see Platelets go up either.

MDSC - Myeloid-derived suppressor cells - these contribute negatively to survival of cancer patients. MDSC's can reduce the effectiveness of Checkpoint inhibitors as well. You want to down regulate PDE 4 & 5 (Phosphodiesterase) which results in a reduction of MDSC. Caffeinated Green Tea Extracts - 40 - 50% epigallocatechin gallate (EGCG) and Coleus Forskholii (Forskolin) down regulate this.

Restoring PTEN is very important - mutations of PTEN are present in aggressive tumors. Loss of it activates numerous cancer growth factors - NF-kB, EGFR, COX-2, PI3K/Akt. When it's working right it suppresses cancer it up regulates the positive gene p.27 resulting in decreased proliferation and an increase in apoptosis (cellular suicide in cancer cells). These natural compounds activate PTEN in a positive way: Quercetin, resveratatrol, thymoquinone (Black Seed Oil), Sulphoraphene (Broccoli seed extracts and cabbage family vegetables, fish oil,

luteolin (radicchio, sweet bell peppers,Shishito and other hot peppers, celery, chicory greens, pumpkin, red leaf lettuce, artichoke, kohlrabi) ,and phytoestrogens. Also Honokiol (Magnolia Bark), Curcumin, Astragalus, Pterostilbene, Milk Thistle

Transforming Growth Factor - b(TGF-b)
This factor TGF-b - plays a key role in tumor immune escape. It is increased in the serum of cancer patients and elevated levels correlate with systemic inhibition of the immune system and poor prognosis. It is a very potent immunosuppressive cytokine involved in suppression of tumor immunity. Suppressing this factor is important in helping checkpoint inhibitors work better.
These are the Botanical suppressors of TGF-b1
Curcumin, Green Tea extract, Green tea and Luteolin, Grape seed extract, Reishi extract, Astragalus, and Salvia miltiorrhiza, Withania somniferea extract (Ashwhaghanda), Silibinin (Milk Thistle extract)
TGF-b1 expression is remarkably inhibited by Astragalus polysaccharide (APS)
Chinese Scullcap (Baicalin) inhibit TGF-b1,Ginger compound zingerone inhibits TGF-b1. 6-shogaol increased E-cadherin. Propolis and Sarsaparilla root (Smilax) lower TGF-b1

JAK-STAT pathway - TGF-b activates JAK1-STAT3 - the natural compounds that target the JAK/STAT pathway are - Curcumin, Parthenolide (Feverfew), Guggulsterone, Piceatannol, Ursolic acid (Rosemary, Sage, Holy Basil). Epimedium (Horny Goat weed), Sernoa Repens (Saw Palmetto), Ginseng, Boswellic acids, Andrographolide, Beta-Escin (Horse Chestnut), NDGA (Chapparal), Honokiol (Magnolia).
Targeting JAK 2 and JAK 3 - Leptin activates JAK 2, JAK 1 down regulating all of these are helpful. Getting JAK 3 to be “Wild Type” is a sign the pathway is acting normally - this is the goal you want to get.

MTOR inhibition - MTOR up regulation can stimulate tumor growth.
PI3K pathway can be mutated in tumors - Taking 1mg of Rapamyacin an antibiotic that can be prescribed it can be combined with other things - There are 70 natural compounds that down regulate **MTOR**
These are the compounds that inhibit PI3-K/mTOR in cancer: Black seed oil, Quercetin, Boswellia, Pterostilbene, Apignin (Propolis, Chamomile, Celery), Berberine, Forskolin, Diosgenin (Wild Yam), Genistein (femented soy), Rhodiola, Milk Thistle extract, Licorice, Chinese Scullcap.

TNF alpha - is another growth factor cancer uses — copper chelation (lowering copper) down regulates this. IL-1 inhibition - **IL1 (Interleukin-1)** affects the growth of **VEGF** (vascular endothelial growth factor) stimulates the growth of blood vessels that feed tumor growth and it can activate **NFkB**
IL-1 plays a part of autoimmune and autoimmune inflammation - down regulating this is important with checkpoint inhibitors. **NFKappa B** (the master signaling system that turns on inflammation in the body) **NLRP3 - Inflammasome** - dampening this is important in lowering inflammation. All of these pathways should be down regulated
<u>These natural compounds all lower NLRP3 Inflammasome-mediated IL-1</u>
<u>Aloe Vera extract, Aloe emodin, Curcumin, EGCG (Green Tea), Ginseng,Propolis, Quercetin, Resveratrol.</u>

IL-1 is very important it is as big as NFKappa B to work with
Inflammasome NRP3 is the center of IL-1 a major inflammatory pathway
Supression of IL-1 inhibits TREG migration. IL-1 is the trigger to the TREGS

Melatonin is partially responsible for inhibiting cancer cell growth, by regulating Interleukin-2, helping Cytotoxic T class and KN cells. *Using low dose 1 - 3mg at bedtime can be supportive.*

Tumors produce **PIBF** - **progesterone induced blocking factor** to keep the immune system from recognizing it - suppressing it may help NK cells. Progesterone is tumor promoting
Suppressing COX-2 - COX-2 stimulates TREGS - Turmeric (Curcumin), Resveratrol, Boswellia, Fish Oils, Quercetin all inhibit COX-2. The drug Celebrex specifically inhibits this pathway.

Bloodwork - CBC, Liver, Thyroid, hsCRP, LDH and metabolic panels should be obtained at each treatment and every 6-12 weeks for 6 months post treatment in all patients receiving immune checkpoint inhibitors.
ACTH and cortisol should also be checked in patients with fatigue and nonspecific symptoms, as well as testosterone and DHEA Sulfate.
LDH can be a marker of immune suppression in cancer. LDH is both a metabolic and an immune surveillance prognostic biomarker and its elevation is a harbinger of negative outcome in both solid and hematologic neoplasms.
Get Copper - Ceruloplasmin done every 3 months.
Get Fibrinogen run - Fibrinogen levels need to be in the normal range low normal is best — high platelets and high fibrin increase the risk of blood clots. **These natural compounds lower fibrinogen levels:** Salvia Methorriza, Ginkgo, Saffron and Fish Oils also garlic, turmeric, ginger, and Vitamin E

<u>Disease can get worse before it gets better</u> - the immune system is invading the tumor and it swells and gets more inflamed as it gets attacked.

Getting a skin rash as a sign of the positive response to the immunotherapy -
<u>Quercetin</u> can help with this positive symptom **-** It works well with skin related rashes.
In bloodwork look for elevated eosinophils caused by the medications and a hyper stimulation of immunity. Skin rash can be a sign of elevated eosinophils.

Auto-immunity is one of the biggest problems with PDL1 inhibitor drugs - patients can often get colitis, thyroiditis, hepatitis. Caused by shutting down the regulatory T-Cells.

Auto Immune related issues with Immunotherapy:
Renal: Nephritis
Adrenal: Insufficiency
Gastrointestinal: Colitis
Liver: Hepatitis
Skin: Dermatitis exfoliative, Vitiligo, Alopecia, Dry Mouth
Eye: Uveitis, Iritis
Endocrine: Hypo or Hyper thyroids, Adrenal insufficiency, Hypophysisis, Autoimmune diabetes, Pancreatitis
Lung: less than 5% can get Pneumonitis
Cardiac: Myocarditis
Neurologic: Neuropathy, Guillain-Barre, Myasthenia gravis like syndrome
Bone and joint: Arthralgia

Key Synergistic Pathways you want to combine with PD-L1 Inhibitors
1. Vagus Nerve activation - get your nervous system de-stressed - be in parasympathetic response state as much as possible. Staying in a state of gratitude helps activate the vagal nerve.

2. Get your Gut healthy - pre and probiotics read the handout “Let’s Get Cultured” for dietary ideas in order to support gut health. Avoid glyphosate sprayed foods ie.Roundup - eat only organic wheat, soy, corn, oats and dried beans - glyphosate is an anti-biotic and kills your microbiome.
3. HDAC (Histone D acetylense) Inhibition - use Ghee ie. Clarified butter in the diet - fiber promotes Butyrate and ITC’s - Broccoli, Cabbage family - Natura Cell Guardian is the formula with all the Broccoli like compounds ITC’s, Sulforophane ect.
4. Target Hypoxia and Lactic acid - check your pH (you can purchase nitrazine paper pH testing paper or strips at your health foods store or a pharmacy) and get more alkaline (mineral rich diets promote alkalinity) WIM Hoff breathing can get you alkaline quickly. CardioVascular research Tri-Salts as a supplement can help. Loads of vegetables in the diet. Potassium Bicarbonate works really well you can order it online. *Get the handout on checking your urine pH.*
5. Immune Biological Modifiers - Endocrine support - Herbal Adaptagens, Mushrooms.
6. Buffer Inflammation - Curcumin, Boswellia, Fish Oils - Natura Botanical Treasures + Natura Inflammaway.

Beta Blockers may improve the efficacy of anti-PD-1 checkpoint blockade in cancer patients by reducing stress hormones. With lower stress (reducing Beta-AR signaling) led to increased intratumoral frequency of CD8+ T cells with an effector phenotype. It also decreased expression of PD-1. *Talk to your oncologist about this*
Plaquinol combined with other drugs can work very well

Diet:
<u>The single most important thing that helps with a positive response to checkpoint inhibitors is the microbiome ie. Microbiota</u>
You have to have a diverse and healthy microbiome to get great results with Immunotherapy -

Read my handout Let’s Get Cultured to learn what to eat to support the microbiome

Probiotic Supplements:
Lactobacillus Rhamnosis GG is an important strain - make sure its part of a probiotic supplement. Aloe Vera Juice can act like a probiotic too.
Oral administration of Bifidobacterium alone improved tumor control to the same degree as PD-L1- specific antibody therapy, and combination treatment nearly abolished tumor outgrowth - it helps dendritic cell function leading to enhanced CD8(+) T cell priming and accumulation in the tumor microenvironment mediated the effect

Important foods to eat: Yogurt, Kefir, Lassi, Sauerkraut, Kimchi, refrigerated pickles, dark chocolate, miso and tempeh. A high fiber diet increases FP - Faecalibacterium prausnitzii (one of the most important probiotic species for immunity) (Kiwi fruit especially Gold Kiwi helps FP along with pomegranate and all high polyphenol foods) and Bifidobacterium and Lactobacilus species. Lactobacillus rhamnosus induces TH1- increasing T-helper type 1 immunity.
Parmigiano Reggiano cheese can have up to 10 million CFU of viable lactic acid bacteria per gram when you it it.
Jerusalem Arichoke - is an excellent pre-biotic. High in FOS - you can bake it in the oven like baked potatoes or grate it raw for a flavor like water chestnuts. Chicory, Bananas, Organic Oats (non-organic Oats are heavily sprayed with Glyphosate (Roundup) which kills the biome in the gut. Asparagus, Jicama and Artichokes.
Dark Chocolate is a prebiotic - it is rich in polyphenols including procyanidins,. Cocoa consumption increases healthy flora especially bifidobacteria and lactobacilli. Dark chocolate protects against stress and increases nitric oxide supporting the heart. It also inhibits cancer.

Black Rice which is rich in gamma propanol increases the cytolytic activity of scenic natural killer cells. VEG-F, COX-2 and 5-LOX are also reduced.
HDAC (Histone deacetylase) Inhibition enhances immunotherapy with PD-1 Blockade. - Natural HDAC inhibitors include butyrate (Ghee made from grass fed butter) and a high fiber diet, and Broccoli compounds ITCs: diallyl disulfide (garlic), and sulforaphane.
HDAC inhibition ups p21 and p27 (beneficial anti-cancer genes) causing tumor growth arrest and apoptosis.
Emmentaler Swiss cheese is high in propionic acid a Short-Chain fatty acid supports HDAC inhibition.
100% organic whole grain fibers produce more Short chain fatty acids. Kamut (Khorasan wheat) is particularly good much better than regular wheat. Look at whole grain organic kamut pasta too. Sourdough bread is more digestible than regular bread make sure its organic. It lowers inflammatory cytokines - IL-6, IL-12 and TNF-alpha
Acetic acid - Organic Apple Cider Vinegar with the mother ie. Braggs helps SCFA's (short chain fatty acids) - Apple Cider Vinegar is also a probiotic stimulant

Astragalus is one of the best botanicals to use - it helps the PDL1 inhibitor and helps prevent auto-immunity. Regulatory T-Cells they stop auto-immunity. It down regulates the adversary TREG cells and allows the influx of cytotoxic T lymphocytes into the cancer. Astragalus activates IL-2 and Interferon Alpha and other cytokines as well. It increases and strengthens Natural Killer Cells and Cytotoxic T cells. It has anti-tumor and anti-angiogenic activity it enhances and balances Th1 and Th2. It nourishes the Bone marrow and protects the liver, kidney and heart. It helps normalize the p53 gene (the guardian of keeping cells normal and not mutating to cancer)

Turmeric extracts - Curcumin - taken before bed enhances it's anti-cancer properties and might clinically be relative to a better overall enhanced anti-tumor effect.

Quercetin can alter the PH of a tumor microenvironment
* It is a potent inhibitor of PI3-k/mTOR tumor signaling
* Specific down regulates C-MYC - master oncogene controller of tumor glycolysis (Vit D also does this)
* Is a potent inhibitor of lactate transport in tumors
* Inhibits tumor glycolysis
* Significant potentiation of hyperthermia-induced cytotoxicity (take a big dose before a sauna or hot bath)
* Daily dosage 2 - 3 grams
* It synergizes with curcumin, green tea, crucifers, and resveratrol. Ie Botanical Treasures + Cell Guardian.

Resveratrol suppresses IL-1beta - this affects NF-kB. It also inhibits the expression of COX-2, MMP-9 and VEGF. Supports the activity of the NK cells (Natural Keller Cells)
Pterostilbene a phytoalexin has less research but might be even more potent.
Curcumin and Resveratrol are synergistic at inhibiting IL-1 beta induced NFkB mediated inflammation and apoptosis
Berberine down regulates IL-1 beta
Zinc is commonly deficient along with Magnesium and B6 are critically important -
You cannot have a healthy functioning immune system without adequate zinc.
9 out of 10 cancer patients have high copper and low zinc.
Donnie has his patients take it between meals and if the level is out of balance he will have them take it 3x a day (75mg total) for 8 to 12 weeks and recheck the cerulaplasmin level
Some people he has to even bump that up. You can use Molybednum to help zinc get rid of excessive copper.

Fish Oils - EPA/DHA - lower IL-1

Specific plants:

Echinacea - activates the immune system to fight cancer. It is a very important herb in helping PDL-1 and other Checkpoint inhibitors work better. It supports activating the immune response which is activated by these drugs so in essence it partners with them supporting the immune systems ability to attack the cancer.

* It enhances NK (Natural Killer) cells - it may be the best botanical for this.
* Normalizes Th1 and Th2 cytokine production
* Anti-Hyaluronidase - making it harder for cancer to spread into adjacent tissue
* Mediates apoptosis / cytotoxic effects
* Down-regulates TNF-a and Bcl-2 through caspase 3/7
* Profoundly Neuroprotective
* Modulates human cytotoxic T-cell cytokine response:Boost IL-2 and IF-alpha
* Decreased the number and function of Tregs, in association with the enhanced feeder function of CD4 antigen-presenting cells.

Reishi Mushroom is very important in helping to activate the immune system - you have to have very high quality Reshi has to have both high amounts of beta glucans polysaccharides and triterpenes. Donald Yance adds it to his Mushroom formula that contains a variety of mushrooms. *See the Natura product handout sheet for more info Mushroom Complete.* It does all the right things for immunity - up regulates what is needed and down regulates what isn't.

Albizia - elevates the mood and promotes NK cell activity and T-cell activity. Inhibits VEGF activity. Anti-angiogenic.
Magnolia Honokiol - Immune modulating, anti-inflammatory (one of the most potent), anti-tumor
Kava has numerous anti-stress and anti-cancer activity
Saffron - incredible blood moving and oxygen enhancing properties and anti-depressant effects - it works like Lovonox for blood clot prevention (H-factor)- it doesn't promote abnormal bleeding. It buffers inflammation.
St. John's Wort - numerous anti-cancer properties
Rauffia Serpentina - a powerful lowerer of the sympathetic response enhances GEMZAR
Shatavari - T-cell activator
Cat's Claw - great with auto-immunity especially with Crohn's and UC.
Ligustrum works well with Astragalus
Aloe Vera an immune modulator - ACEmannan - is the best form. Enhances cytotoxic T-Cells - it functions as a probiotic