Abstract No. 5535: Non-invasive cellular nano-permeabilization to enhance drug delivery and improve therapeutic outcome in solid tumors: Mitigating the path to destruction

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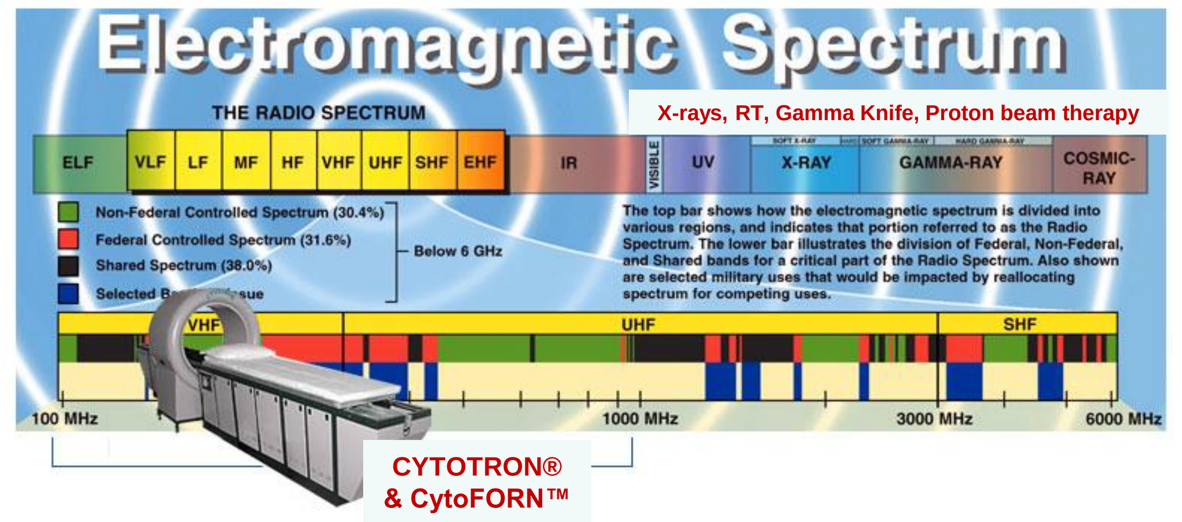
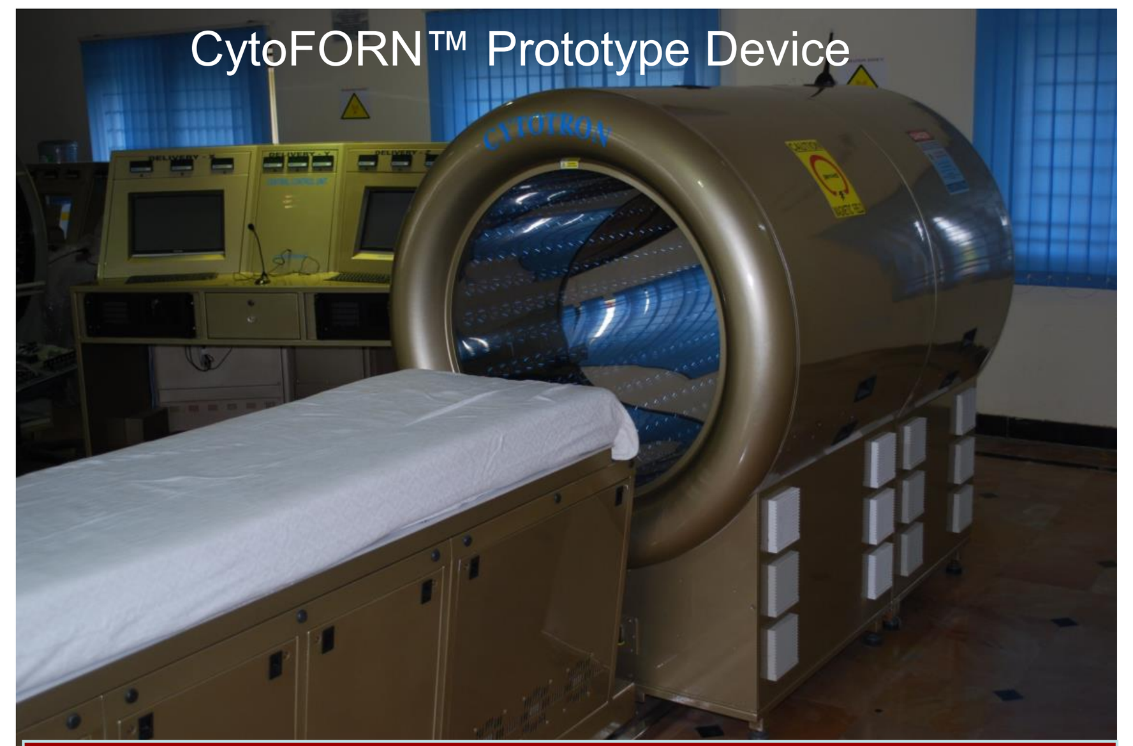
Abstract

Quantum Magnetic Resonance Therapy (QMRT) is a device-mediated, innovative therapeutic modality for cancer, currently in the clinical stage of development. This platform technology can also be used to deliver an electromagnetic force with strong, embedded, variable radio signals to induce Focused Resonance Nano-permeabilization (FORN) to selectively target multiple lesions in the whole body with parenteral or oral drugs used in standard of care cancer treatment. Transient permeabilization of cells by radiofrequency (RF) mediated pulses to target lesions allows drug(s) to be optimally internalized based on pharmacodynamic and pharmacokinetic parameters like drug molecular weight, peak plasma concentration of drug/active metabolite and drug wash out time. FORN has been used in a pilot study in a variety of solid tumors including treatment refractory pediatric medulloblastoma, recurrent adult glioblastoma, metastatic breast, ovarian, recurrent metastatic nasopharyngeal carcinoma and relapsed metastatic osteosarcoma; in patients who were administered protocol-driven chemotherapy under routine standard of care management. The combination of chemotherapy with FORN significantly reduced drug-induced cytotoxicity primarily associated with myelosuppression and other commonly encountered adverse effects during conventional treatment. Improved clinical benefit and efficacy was established using imaging criteria (MRI and or PET-CT based PERCIST 1.0 criteria), biomarker evaluation as well as a comparison of chemotherapy cycles that were previously administered without concurrent FORN.

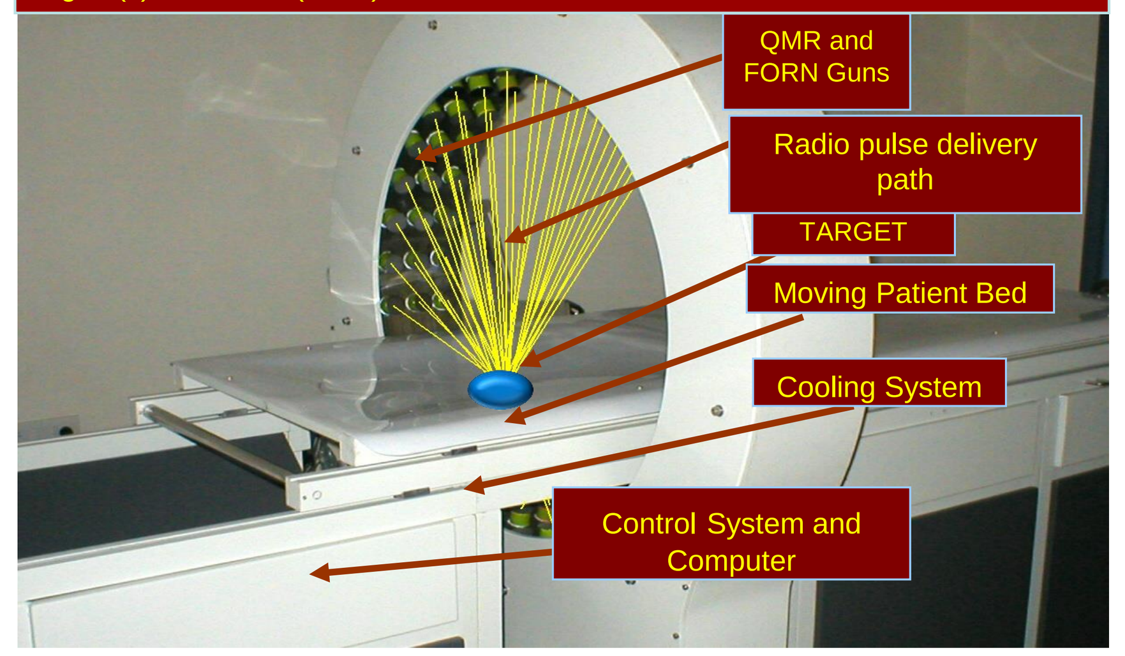
All solid tumors, irrespective of pathological sub-type or grade, can be resonated with customized, high, instantaneous magnetic fields and radio frequency (RF), followed by nano second signals which penetrate only resonating cells to induce cellular nanopermeabilization, non-invasively. This protocol allows for extremely accurate QMR dosing for therapeutic purposes. FORN can be achieved using a safe, non-ionizing extraneous RF and MR source to permeate tractable and intractable tumors by creating molecular dimension-specific transient pores in the cell membrane of tumor cells. Both large and small molecule (oral and parenteral) therapeutics can be safely targeted and delivered using FORN. It is known that electroporation of cultured cells potentiates cytotoxicity of various chemotherapy agents and other targeted molecules. This potentiation can be highly customized using FORN and the pharmacokinetics of any drug administered. FORN technology can potentiate antitumor effectiveness of drugs several fold and can be precisely localized and targeted without implanting any electrodes, probes or invasive nano-particles to deliver drug payloads.

Technology Background & Objectives





Cross section of one axis in the Gantry shows an assembly of RF guns with near-field antennae that deliver precisely timed radio pulses to target area or region(s) of interest (ROIs)



In 1987, the Scalene Centre for Research and Development (S-CARD), initiated a project to study the effect of modulated radio frequency (RF) in the unexplored frequency band of 30kHz to 300MHz. Rotational Field Quantum Magnetic Resonance (RFQMR®) technology and Quantum Magnetic Resonance Therapy (QMRT®) was developed, operating at the safe, non-ionizing end of the EM Spectrum.

FORN Technology Basics

- Specialized antennae in the device gantry non-invasively deliver short bursts of high intensity radio pulses *in vivo* to any anatomical site without the use of probes
- The process is akin to 'electroporation' of the lipid bilayer, which in the application of FORN is totally non-invasive
- Instantaneous mode magnetic resonance is coupled with highly cell and site specific radio modulation based on MRI-derived tissue specific Proton Density (PD), permittivity, conductivity and depth of penetration (DoP) of tissues in gun path.
- Radio pulses are used to generate drug molecular dimension-specific temporary pores in the cell membrane to allow targeted delivery to multiple lesions in the body simultaneously, during peak plasma drug concentration.
- Nano-permeabilization is timed for specific durations (nano-second increments) based on the size of the drug molecule
- When Radio-pulsing is withdrawn the temporary pores re-align and drug is internalized.
- In the clinic, this protocol needs to be precisely timed and administered only on the days of chemotherapy, in cooperation with the treating medical oncologist.

Primary Objectives

- Enabling Cancer Chemotherapy with the use of Focused Resonance Nano-permeabilization (FORN) by impacting efficacy, reducing systemic toxicities, affording pain relief & palliation to improve Quality of Life
- Envision Chemotherapy + FORN to emerge as an adjuvant modality/salvage cancer therapy both in primary and metastatic disease
- Test drug focusing and targeted delivery with FORN in patients with advanced loco-regional and metastatic disease, on diverse oral and systemic chemotherapy regimens.
- Fulfil the unmet need of the proverbial "magic bullet" using FORN to target a variety of advanced solid tumors irrespective of pathological sub-type or anatomical location, stage/ grade of the disease.

Secondary Objectives

- Position FORN technology squarely within the drug development continuum so as to positively impact new drug discovery and rejuvenate pharma pipe lines
- Salvage potentially valuable cancer drugs, shelved due to early/late stage failures on account of dose-limiting toxicities

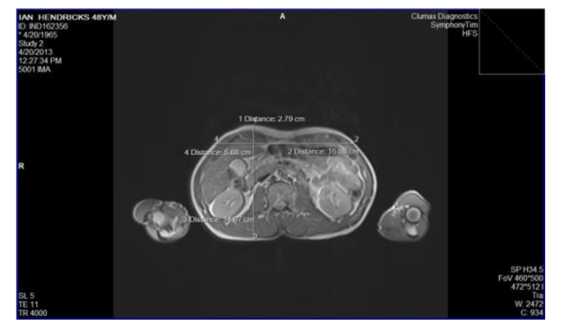
Methods

CytoFORN™ enabled Nano-permeabilization

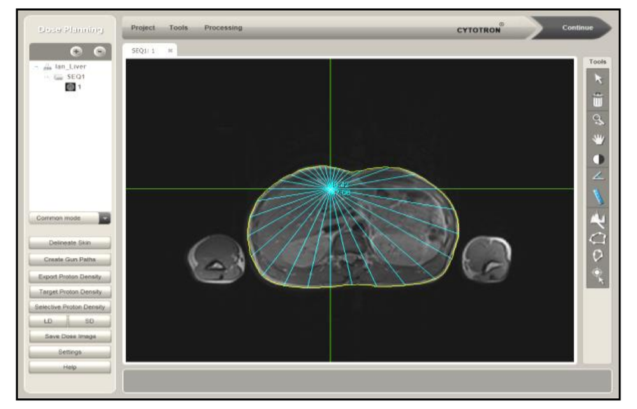
Potentiation can be tightly controlled by the Cytotron by adjusting delivery parameters like molecular mass of the drug, the peak plasma concentration, drug wash out time, total tissue volume, cell membrane characteristics etc.

- FORN can potentiate antitumor effectiveness of drugs (10 to 70 fold) and can be highly localized and targeted *in vivo* without implanting electrodes or probes into the body.
- Short bursts of high intensity radio pulses create temporary channels/pores which close when the signal is removed after the drug passes through the cell membrane.
- Cell permeabilization occurs only in those cells or tissues that are in resonance and attain the required beat frequency.
- Non-resonating cells do not respond to FORN, as they are in their resting state.

Dose Planning & Simulation



- Treatment planning and dosimetry is based on weighted PD sequence
- The Radiologist prepares the planning film, with measurements of the lesion marked on the film as well as on a Compact Disc (CD)
- The CD with images of specific Region(s) of interest is loaded into the control computer.
- Dosimetry is done separately for each lesion with gun paths of specific high intensity nano second duration radio pulses
- RF guns in specified axis/axes for respective lesions are computed automatically at 360 degrees around the lesion (s)



Chemotherapy scheduling before FORN

- Tumor targeting and dosimetry is derived from weighted PD sequence data for the whole organ or region. Ideally having a PET-CT scan prior to dosimetry planning helps identify and target lesions anywhere in the whole body simultaneously.
- Cell size, radius, cell wall thickness is determined from photomicrographs prepared from cell samples obtained during biopsy or from reference standards.
- Molecular weight of the drug, peak plasma concentration, route, timing of delivery and dosage of the drug are determined in discussion with the oncologist.
- Patient is administered the required dose of the drug to be permeated X-minutes before applying FORN protocol (X=time to reach peak plasma concentration).
- Exposure: Y-hours/day for Z-days. Y is time period required for the trans-permeablization of maximum drug molecules of the drug of interest ; Z is number of cycles of the drug. Periodic assessment is done using ultrasound, CT, MRI or PET scan.

Clinical Investigation Plan (CIP)

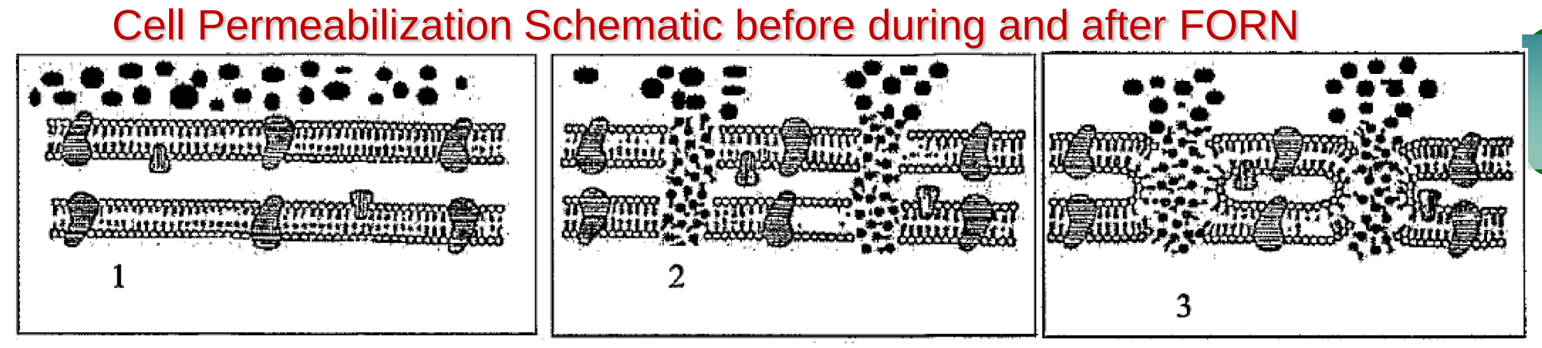
- Reduce systemic toxicities of standard of care drugs within effective therapeutic windows in patients who have failed 3rd and 4th line therapies and presented with advanced disease.
- Improve therapeutic outcomes with extended efficacy end points like i) time to progression ii) disease free survival using RECIST 2.1 and PERCIST 1.0.
- Simultaneously manage chronic pain, effectively palliate, & improve quality of life while extending survival.
- Cohort consisted of volunteer participants with recurring, advanced metastatic disease, overcoming very serious adverse effects.
- A Nasopharyngeal carcinoma patient-with loco-regional recurrence and multiple metastases-being treated at a local comprehensive cancer treatment center in Bengaluru is show-cased here

Region	ID No.	Axis Fired
Chemo Cycle 2 (2 hrs)		
Nasopharyngeal Area	042	D & E
Mediastinal LN	043	C
Liver	044	B
Left Ilium	045	A
Chemo Cycle 3 (2 hrs)		
Nasopharyngeal Area	042	I
Mediastinal LN	043	H
Liver	046	G
Left Ilium	045	F to A
Chemo Cycle 4 (2 hrs.)		
Nasopharyngeal Area	042	E
Mediastinal LN	043	D
Liver	046	C
Left Ilium	045	A & B
Chemo Cycle 5 (2 hrs.)		
Nasopharyngeal Area	042	I
Mediastinal LN	043	H
D8 vertebrae	047	G
Left Ilium	048	F to A
Chemo Cycle 6 (2 hrs.)		
Nasopharyngeal Area	042	E
Mediastinal LN	043	D
Liver	046	B
D8 vertebrae	049	C
Left Ilium	050	A
Chemo Cycle 7 (1st hr.)		
Nasopharyngeal Area	042	I & H
Mediastinal LN	051	G
Liver	046	F
Left ilium	053	E to A
Chemo Cycle 7 (2nd hr.)		
Nasopharyngeal Area	042	I
Mediastinal LN	051	H
D8 vertebrae	052	G
Left ilium	053	F to A

Table shows the chemo-cycles combined with FORN using all 9 axes (A-I) of the whole body CytoFORN device used to target the ROIs

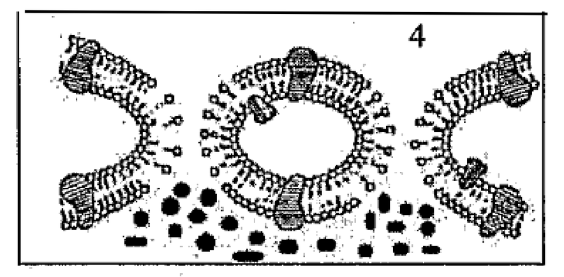
- At precise times after administration of chemotherapy, radio-pulses are delivered to ROIs, to span peak plasma concentrations of infused drugs
- Radio-pulses are delivered in the presence of an instantaneous magnetic field, to create temporary, drug molecular weight-specific nano-pores in the cell membrane of target lesions
- The pores remain open for the duration of peak plasma concentration of given drug (s)
- Radio-pulsing/nano-poration is stopped and drug (s) internalized

Cell Permeabilization Schematic before during and after FORN

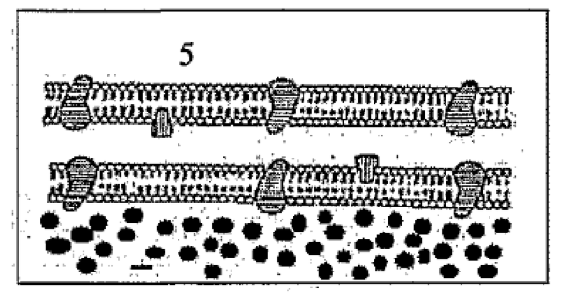


Drug molecules around cells with in-tact cell membrane

During FORN treatment drug-size specific pores are created



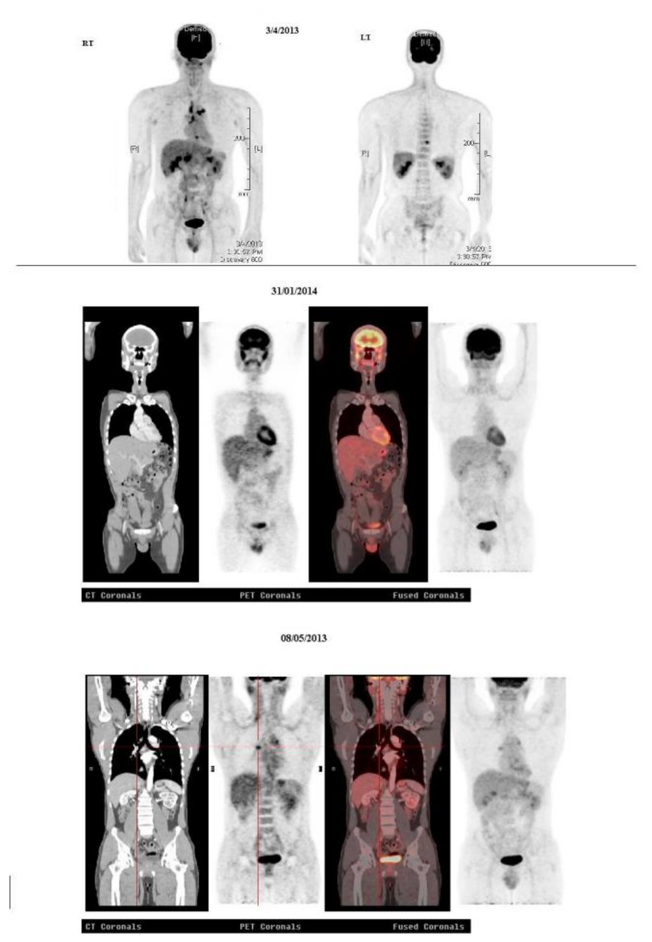
Start of reconstruction of cell membrane after FORN



Drug is internalized, reconstruction complete and cell membrane is intact

Results

PET-CT outcome after 6 chemo +FORN cycles



PREVIOUSLY NOTED NODES	PET CT FINDINGS ON		
LOCATION	04/03/2013	05/08/2013	31/01/2014
PREVASCULAR NODES	Measured size - 3.6x1.4 and SUV max uptake - 6.2	Measured size – 2.2x1.1 and SUV max uptake - 3.1	Not seen
PRECARINAL NODES	SUV max uptake - 5.2	Measured size – 1.7x1.2 and SUV max uptake- 2.1	Not seen
RIGHT HILAR NODES	Measured size - 1.4X1.5 and SUV max uptake - 2.3	Measured size – 1.3X1.2 and SUV max uptake – 3.1	Not seen
SKELETAL LESIONS	Seen in D10, D3, D4, L5, L3	Resolved in metabolic activity and appears more sclerotic in this study.	Sclerotic lesions are seen in D4-D5, D10, L3, L5 vertebrae and also in Sacrum, left iliac bone and head of left femur
LIVER LESIONS	FDG avid lesion in right lobe of liver	Totally resolved in size and metabolic activity	Non FDG avid hypodense areas in segment VIII and anteriorly in the left lobe involving segment IV,II and III

Study cohort of solid tumor patients

- Recurrent, metastatic nasopharyngeal carcinoma 6 cycles of carboplatin and paclitaxel + FORN
  Outcome: local recurrence, hepatic lesion, mediastinal lymph node and bone metastases resolved.
- Stage 1V Ovarian cancer
  1 cycle of Carboplatin and Gemzar + FORN
  Outcome: Targeted treatment refractory lesion resolved

Relatively reduced cytotoxicity related events compared to just conventional chemo cycles without adjuvant FORN in patients with advanced disease

- Ca Breast with liver, Lung & skeletal mets - Ixempra + Capecitabine
- Ca Breast with liver, pelvic bone, left adrenal & brain mets- Oral Lapatinib and Temezolamide
- Anaplastic Astrocytoma – Oral Temezolamide + Physalis minima
- Pediatric recurrent medulloblastoma-Cyclophosphamide & Etoposide
- Radiation-induced relapsed metastatic osteosarcoma on Sorefinib

FORN-enabled chemotherapy advantage

- FORN enabled chemotherapy-related adverse event evaluation and tumor response reflected improved clinical, anatomical and metabolic outcomes and significantly reduced myelo-suppression.
- Functional Assessment of Cancer Treatment (FACT), Quality of Life (QoL) and Karnofsky Performance Status (KPS) scores reflected overall patient well-being.
- Recurrent, loco-regional disease, nodal, hepatic and skeletal metastases showed dramatic response on PET-CT follow up, based on PERCIST 1.0 criteria

- Systemic circulation of residual drug is apparently reduced due to minimal cytotoxicity seen in routine blood work performed during/between chemo cycles
- No platelet/blood were transfusions required during chemo + FORN cycles
- Extended disease free /progression free survival was noted
- Improved quality of life and pain relief was reported.
- Patient compliance for chemotherapy improved dramatically

Cancer Therapy Challenge and the CytoFORN Solution

- Targeted therapies were supposed to be game-changers
- Several aggressive cancers are chemo/ radio-resistant
- Multi-drug resistance poses a major setback
- Blood brain barrier creates drug delivery issues
- Poor tumor penetration/impermeable large molecule drugs that are otherwise promising e.g. Curcumin
- Limited number of nano-formulations available
- Dose-limiting toxicities prevent dose-dense regimens
- Awaiting genotyping results can delay chemotherapy decisions due to limited availability of sample tumor tissue
- Clinical decision making time constraints
- Concept of "basket clinical trials"- Pooling different tumors irrespective of pathology/markers etc. not in practice today

A Magic Bullet of sorts??

Using proton density measurements to "mark" target lesions (irrespective of solid tumor-type/pathology) and transiently nano-permeating tractable and intractable lesions using pharmacodynamic characteristics of individual drug moieties could help overcome a few of the prevailing barriers…..a modest claim to the proverbial magic bullet in need of extensive cooperative research with big pharma

* Inventor and Patent holder for CYTOTRON® and CytoFORN™ (Cytotron Patent No. US 2007/0208249 A1 and FORN Patent publication No. US 2012/0004591 A1)

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