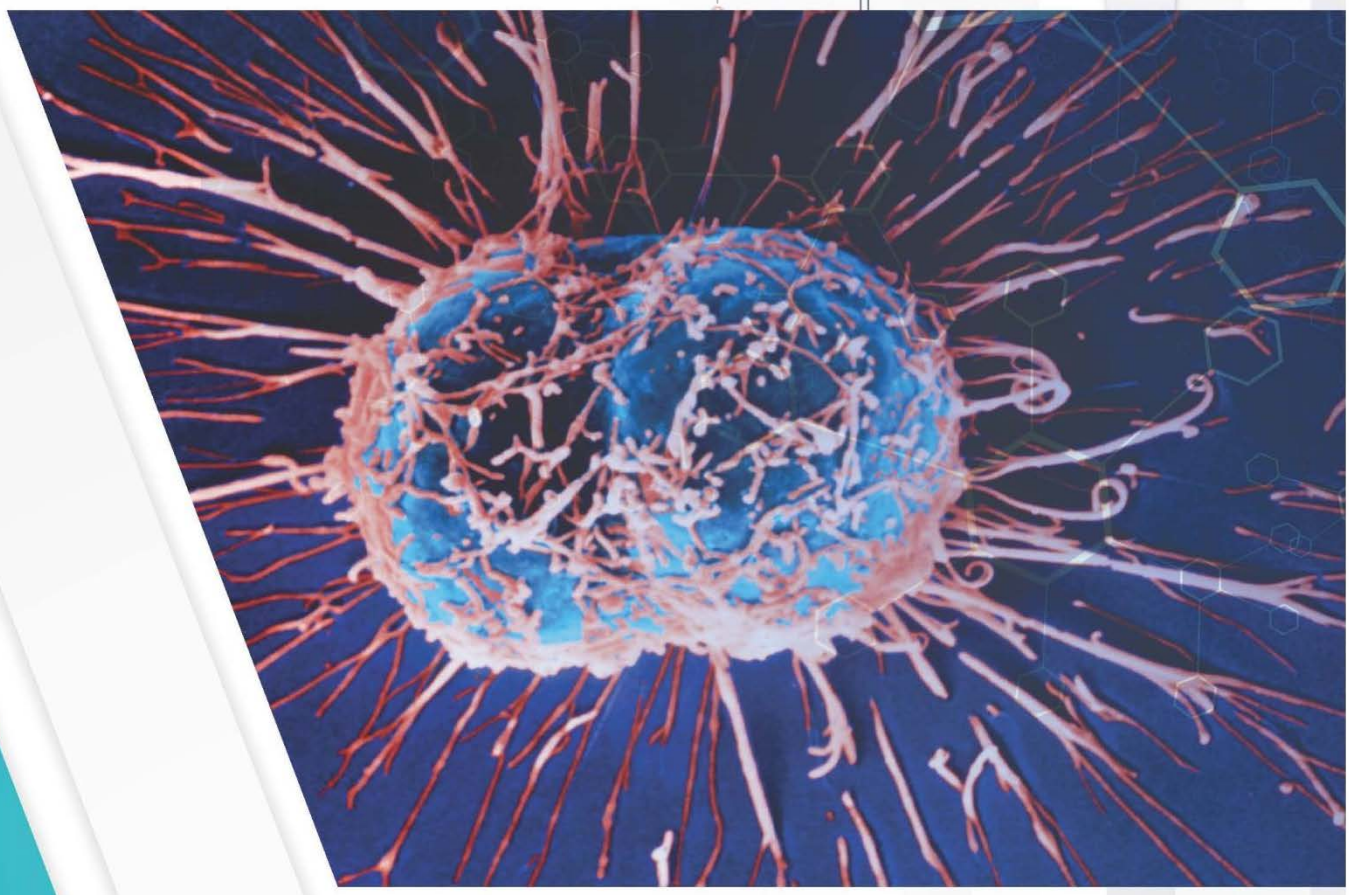
Shréis Scalene Sciences

CELLFORN™

Enhancing Targeted Drug Delivery



Focused Resonance Nano-permeabilization

for Chemo-potentiation and Improved Therapeutic Outcomes in Solid Tumors

In 1987, the Scalene Centre for Advanced 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®) platform technology and Quantum Magnetic Resonance Therapy (QMRT®) was developed, operating at the safe, non-ionizing, non-thermal end of the EM Spectrum.

Focused Resonance Nano-permeabilization (FORN®) is a non-invasive drug focusing and targeted delivery technology based on similar principles of RFQMR® and QMRT®.

- QMRT is a device-mediated, innovative, tissue-engineering based therapeutic modality for degenerative and proliferative diseases like Osteoarthritis and Cancer respectively, currently in clinical stages 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®)
- Multiple lesions can be selectively targeted in the whole body with parenteral or oral drugs used in standards of care cancer treatment
- Transient permeabilization of cells by RF mediated pulses allows drug(s) to be optimally internalized
- The process is driven using pharmacodynamic and pharmacokinetic criteria 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 and ovarian carcinoma, 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 systemic effects during conventional cancer chemotherapy regimens
- 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®

Advantages of FORN® when used with standards of care chemotherapy

- FORN® technology can potentiate antitumor effectiveness of drugs several fold and can be precisely localized and targeted without implanting electrodes, probes or invasive nano-particles carrying drug payloads
- 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 nano-permeabilization, non-invasively
- This protocol allows for extremely accurate QMR dosing for drug delivery purposes to permeate tractable and intractable lesions by creating molecular dimension-specific transient pores in the cell membrane of tumor cells
- Large and small molecule (oral & parenteral) therapeutics can be safely targeted & delivered using FORN®, even to the brain
- 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® based on the pharmacokinetics of the drug of choice

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 the RF gun path
- Radio pulses are used to generate drug molecular dimension-specific temporary pores in the cell membrane, enhancing 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 to be internalized

Primary Objectives with Concurrent CELLFORN in Cancer Medicine

- Enable 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- irrespective of molecular size of oral and systemic chemotherapy regimens
- Fulfil the unmet need of the proverbial pharmacological "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

Primary Objectives for CELLFORN in Cancer Drug Discovery

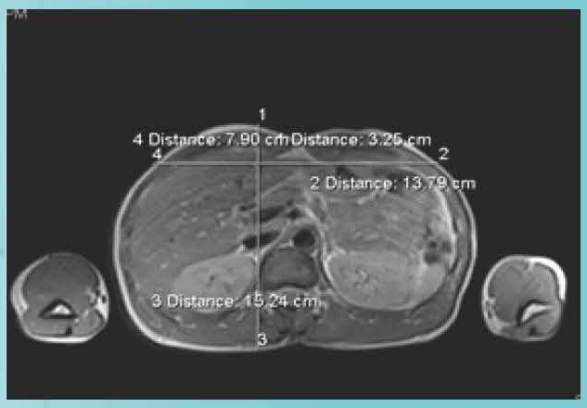
- Position FORN® technology squarely within the drug development continuum so as to positively impact new drug discovery and rejuvenate pharma pipe lines
- Salvage potentially valuable cancer drugs, shelved due to early/late stage failures on account of dose-limiting cyto-toxicities

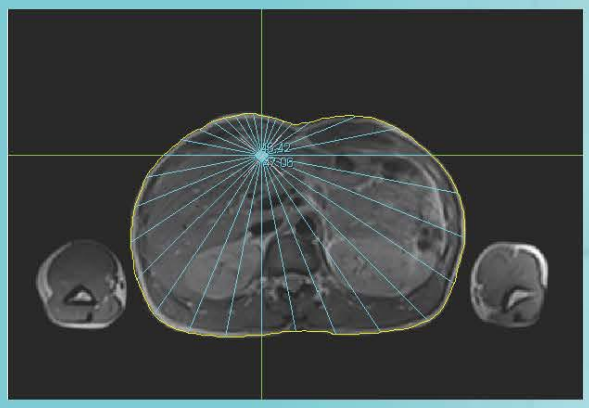
CELLFORN is Precise and Personalized

Drug potentiation can be tightly controlled by FORN® by adjusting delivery parameters based on molecular mass, 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 applied *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 no respond to FORN® as they are in their 'resting' state; naturally protecting surrounding, non-targeted, normal tissues.

Dose Planning & Simulation





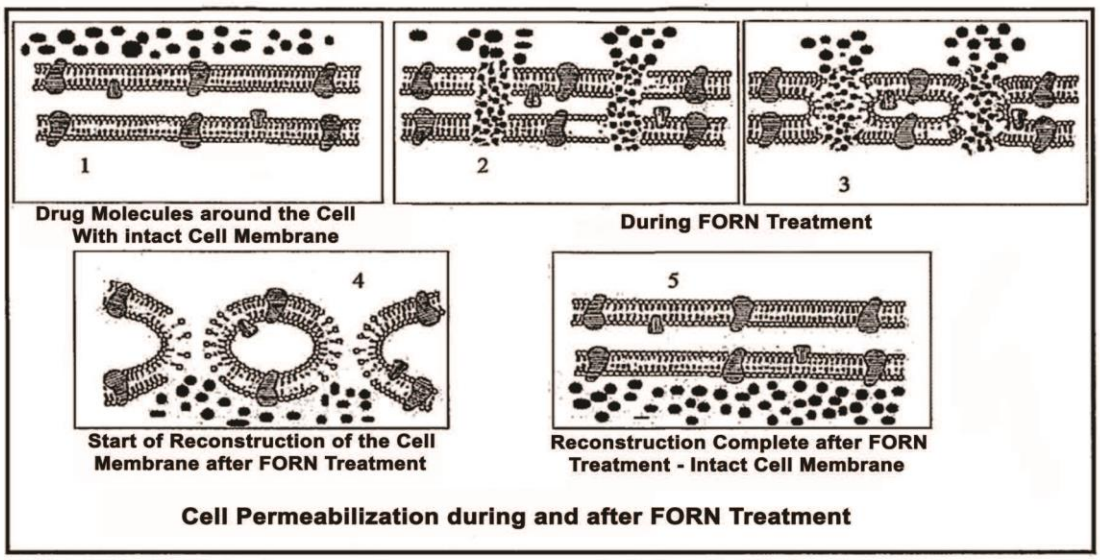
- FORN® planning and dosimetry is based on MRI-derived weighted PD sequence
- The Radiologist prepares the planning film, with measurements of the lesion marked on the film (left frame) and transfers these images onto a Compact Disc (CD)
- The CD with images of specific Region(s) of interest (ROI) is 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) (right frame)

FORN® Protocol

- Ideally having a PET-CT scan prior to dosimetry planning helps identify target lesions anywhere in the whole body, providing a base line of active disease status
- Tumor targeting & dosimetry is based on weighted PD sequence data for the whole organ/region
- Cell size, radius, cell wall thickness is determined from reference standards
- Molecular weight of the drug / metabolites, peak plasma concentration, route, timing of delivery, drug wash out time and dosage of the drug are pre-determined
- Oncologist administers the specified dose of the drug to be permeated X-minutes before applying the FORN® protocol (X=time to reach peak plasma concentration)
- FORN ®Exposure: Patient is placed in the CELLFORN gantry for Y-hours/day for Z-days. Y is time period required for the trans-permeabilization of drug molecules (30 minutes to 2 hours maximum) into the regions of interest during peak plasma concentration; Z is number of cycles of the drug
- Periodic clinical assessment of the patient is done using routine blood chemistry
- Follow up ultrasound, CT, MRI and/or PET-CT is required for tumor effectiveness and outcome analysis

Cell Permeabilization schematic before, during and after FORN®

Patent: WO/2010/106544: A METHOD AND APPARATUS FOR - FOCUSED RESONANCE NANOPERMEABILIZATION (FORN®)



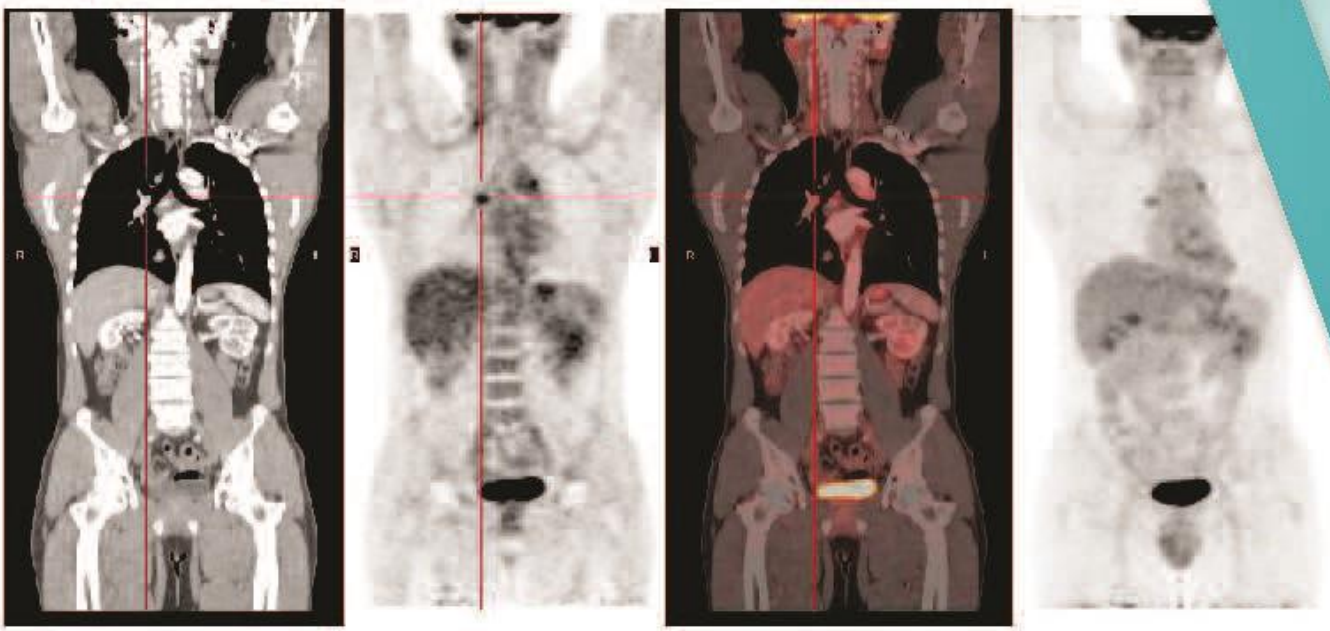
Clinical benefits with concurrent FORN® over conventional Standards of Care chemotherapy regimens

- Reduced systemic toxicities observed within effective therapeutic windows even in patients who had failed 3rd and 4th line therapies and presented with advanced disease
- Improved therapeutic outcomes noted with extended efficacy end points, like
  i) time to progression
  ii) disease free survival using RECIST 2.1 and PERCIST 1.0 criteria
- Simultaneous management of chronic pain, effective palliation and improved quality of life with extended survival was enabled
- Cohort of volunteer participants evaluated had recurring, advanced metastatic disease who experienced none of the serious adverse effects routinely evident with conventional / palliative chemotherapy

Case Study CELLFORN in advanced, recurrent nasopharyngeal carcinoma with multiple metastases

- At precise times after administration of 6 cycles of Carboplatin and Paclitaxel (CBDCA+PC #6), FORN® was delivered to ROIs, to span peak plasma concentrations of infused drugs
- RF pulses were 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 for the duration of peak plasma concentration of given drug (s)
- Radio-pulsing/nano-poration is withdrawn to entrap drug molecules within lesion(s)
- Outcome analysis based on PERCIST 1.0 criteria showed evidence that FORN-mediated drug focusing over 6 cycles of chemotherapy almost completely eliminated the targeted ROIs i.e. relapsed, loco-regional recurrence, liver metastasis, lymph node metastasis and multiple bone metastases

(See original PET-CT images inset below - before and after 6 FORN cycles)



CT Coronals PET Coronals Fused Coronals

FORN® Study cohort of other advanced cancer patients in who primary study objectives were met

- Stage 1V Ovarian cancer on 1 cycle of systemic Carboplatin and Gemzar
- Ca Breast with liver, lung & skeletal metastases on Ixempra + Capecitabine
- Ca Breast with liver, pelvic bone, left adrenal & brain mets on oral Lapatinib and Temozolamide
- Anaplastic Astrocytoma on oral Temozolamide + Physalis minima
- Pediatric recurrent medulloblastoma on systemic Cyclophosphamide & Etoposide
- Radiation-induced relapsed metastatic osteosarcoma on oral Sorefinib

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

- 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 transfusions were 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

Distinct advantages over conventional chemotherapy

- Targeted therapies can be the "game changers" they were meant to be
- Chemo-resistance built up over innumerable cycles can be by-passed
- Multi-drug resistance can be overcome
- Blood brain barrier to drug delivery is no longer a "barrier"
- Poor tumor penetration with impermeable large molecule drugs that are otherwise promising and potent e.g. Curcumin is FORN® -enabled and internalized
- Limitations that not all drugs are nano-formulated is over-ridden
- Dose-dense regimens can be administered without limiting the dose
- Precision drug-pairing based on molecular markers can be side-stepped
- Clinical decision making time constraints are minimal
- The concept of "basket clinical trials"- that all tumors are tractable can be a reality

Is CellFORN 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

FIGURE: 9

FIGURE: 10

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CELLFORN™ - A Breakthrough solution for targeted, personalized, precise Cancer Drug Delivery