Futuristic Toxicology

An effort to Enhance Successful Drug Development By Innovations In Bridging The *in Vitro* / *in vivo* Human Testing Gap

---

Abhay Deshpande, Ph.D.
CEO,
JRF Global

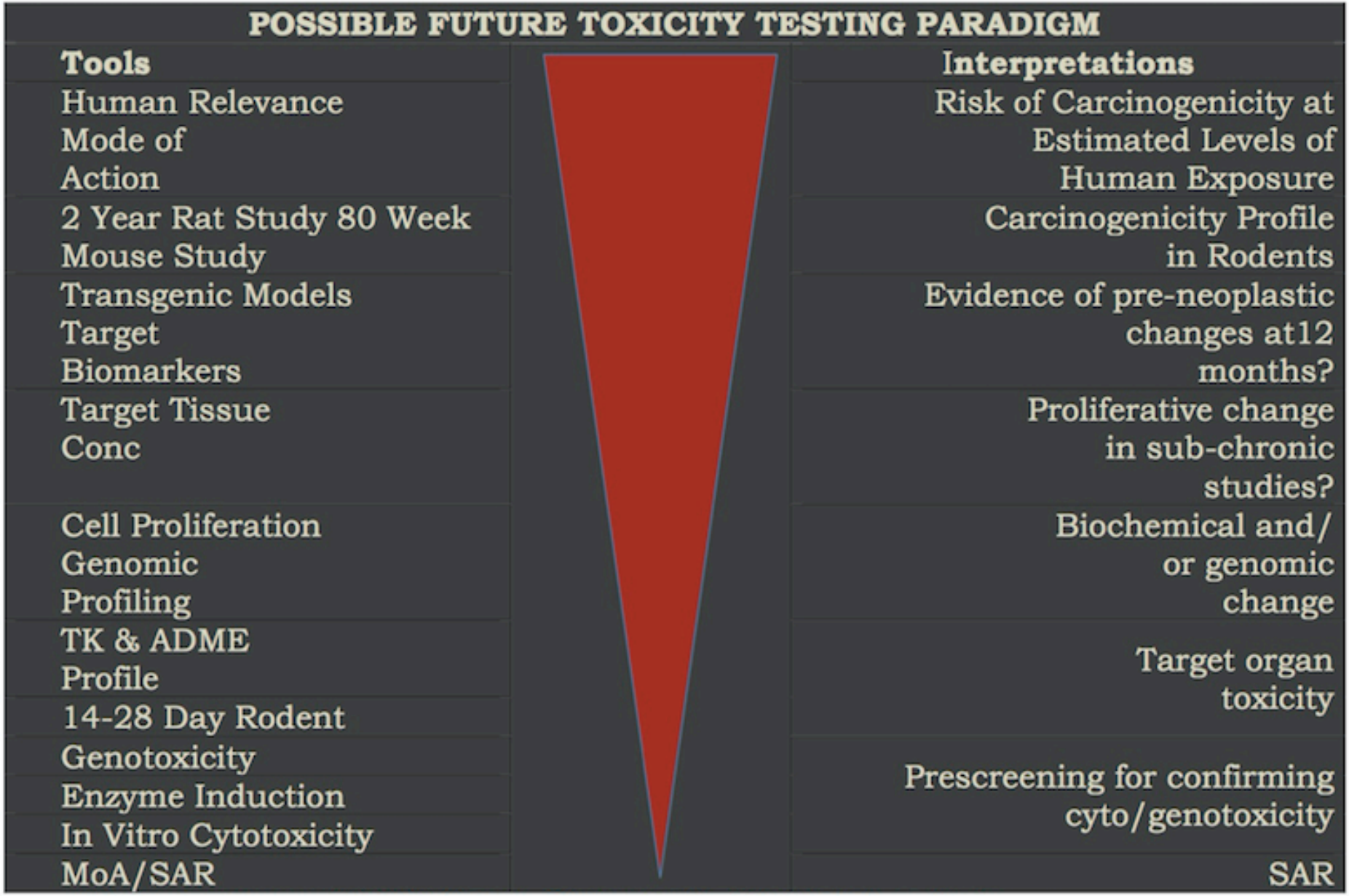
ROSALIND FRANKLIN UNIVERSITY of MEDICINE AND SCIENCE

Sept. 19, 2017

Philosopher John Schaar,

"The future is not some place we are going to, but one we are creating….The paths are not to be found……., but made,

……the activity of making them changes both maker and the destination."



Ref: Dr. Paul Parsons AGCHEM Forum, September 05, 2013 Barcelona, Spain

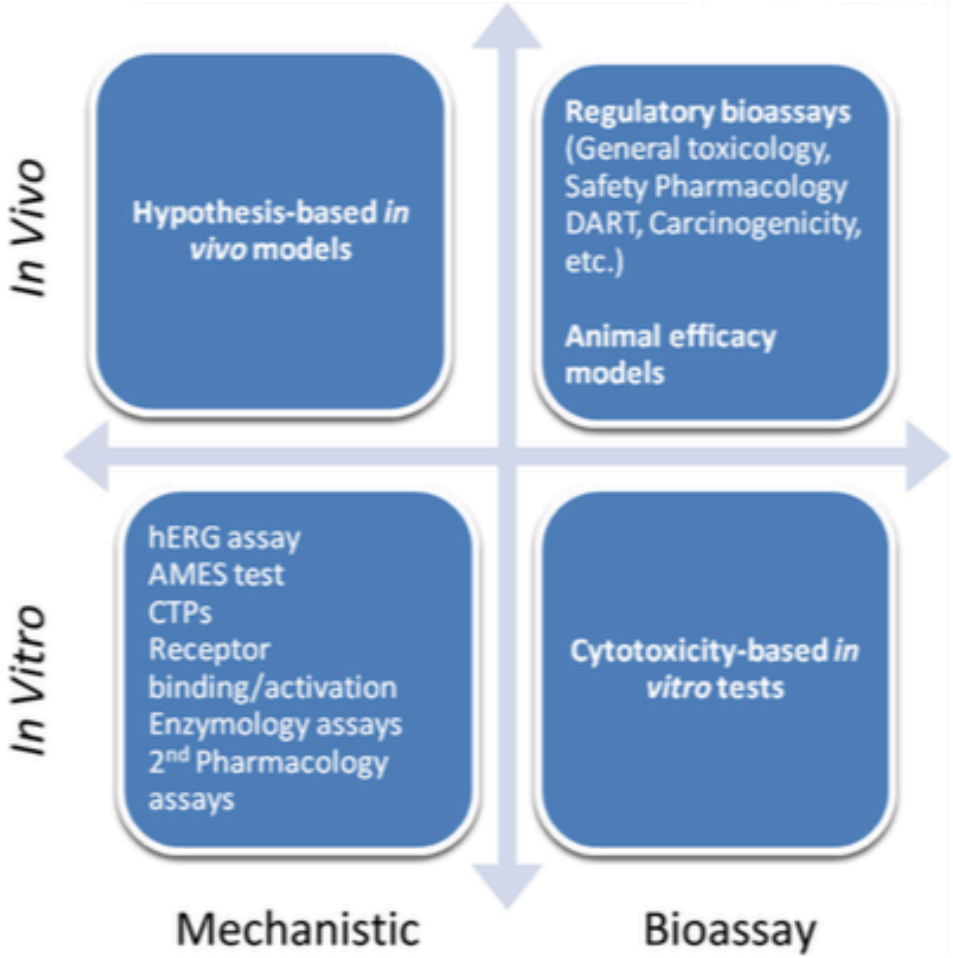


Fig. 1. Examples of *in vitro* and *in vivo* methods. Specific biological mechanisms and holistic bioassays are represented separately. hERG, human Ether-a-Go-go Related Gene; CTPs, phosphocholine cytidylyltransferase; DART, developmental and reproductive toxicity.

Chapman et al; Regulatory Toxicology and Pharmacology 66 (2013) 88–103

Approach….

1. *Comprehensive development of in vitro methods*
2. *Integrate with in vitro and in vivo safety pharmacology*
3. *Optimize animal study designs to "get the best of the least number of animals used"*

Pathway

1. *in vitro* methods must be based on identification of mechanistic end points, useful for predictive toxicology
2. *in vitro* methods for compound screening, in turn saving humongous number of animals, which could have been exposed to the “eliminated candidates”.
3. Predictive toxicology will help accurate lead selection, to minimize the use of animals for drugs which could be identified as destined to fail later in development!

Futuristic Efficacy & Safety evaluation

Developmental phase:

1. Lead identification, selection: *in silico*, *in vitro science*
2. Lead Optimization: Minimal usage of Animals
3. Product Development: Combinatorial tox testing; several experimental parameters in a single test with minimal usage of animals

Successful Drug development

Rationale:

The human needs for safer, smarter chemicals, which are;

- Safe
- Minimal dosages
- metabolites/degradents are safe for the human beings and environment,
- manufactured using energy efficient green chemistries

Rationale:

- Therapeutic target Focus
- Toxico-genomics considerations
- Target specific biomarkers and testing paradigm driven by such biomarkers
  - Liver function (e.g., MAO, transaminases, bilirubin, alkaline phosphatase) kidney function (e.g., serum creatinine, creatinine clearance, cystatin C), skeletal muscle(myoglobin), cardiac muscle injury (CK-MB, troponin I or T), bone-specific alkaline phosphatase).
- Testing paradigm focused parallel testing for species sensitivity/response

List of preliminary assays ……Physico-chemical properties

1. *List of screening assays*
2. *Water solubility*
3. *Solvent solubility*
4. *Partition coefficient*
5. *Dissociation constant*
6. *Permeability using PAMPA (Parallel Artificial Membrane Permeability Assay)*

List of in vitro Assays

1. *Cytotoxicity (CHO K1 & Human Lymphocyte & Hepatocyte)*
2. *Permeability: CaCO-2*
3. *Genotoxicity*
4. *hERG:*
5. *in vitro ADME Tier I and II*
6. *In vitro sensitization*
7. *Endocrine disruption screening: (Aromatase and Androgen + Estrogen receptor binding assays in Rat Cytosol)*

List of in vitro Assays

1. *Zebra fish*
   1. *Acute toxicity*
   2. *Developmental, toxicity*
   3. *Hepatotoxicity*
2. *Mucous membrane sensitization / toxicity for mucous membrane based drug delivery systems*
3. *Phototoxicity/ Photosensitization*
4. *Dermal absorption (for products aimed at dermal application as topical/ drug delivery approach)*

Bridging Tools leading to Predictive Efficacy screening & Toxicology

MODELS ON THE HORIZON

1. *Human and animal primary two / three dimensional cell lines as screening / toxicity assessment tools*
    1. *Hepatocytes*
    2. *Keratinocytes, melanocytes and fibroblasts*
    3. *Cardiomyocytes and fibroblasts*
    4. *Lung (Bronchial/ squamous epithelium, Alveolar Macrophages, Lymph nodes etc*

Bridging Tools leading to Predictive Efficacy screening & Toxicology

MODELS ON THE HORIZON

1. *Human and animal pluripotent stem cells suitably differentiated into target tissues*
    1. *Leukemia efficacy/ toxicity model (Artificial Bone marrow-like environments (ABME by NCCS India)*
    2. *Neuronal, Lung, Cardiomyocytes, hepatocytes, Kidney tissues, Spleen and pancreatic tissues*
    3. *Zebra fish embryo*

List of in vivo Assays

1. *Minimalistic Animal studies;*
2. *MTD coupled with TK*
3. *Safety Pharmacology;*
    1. *hERG,*
    2. *Modified Irwin's,*
    3. *Rodent for Respiratory and CNS*
    4. *Canine CVS*
4. *Dose range finders, 28 days etc.*

Futuristic *in vivo* Safety evaluation

AN INNOVATIVE PROTOCOL FOR EFFICACY AND SAFETY EVALUATION BY INTEGRATION OF *IN VITRO* AND *IN VIVO* TESTING.

Combinatorial Safety Evaluation Paradigm

- *One study protocol, to cover all the phases in life of a mammal….*
- *Begins with adolescence, reproductively matured adult, reproduction, juvenile and the cycle repeats….*
- *Study provides age related changes in important biomarkers, while covering conventional toxicology endpoints and coupling with human relevance!*

Combinatorial Safety Evaluation Paradigm

- *Combination of several studies to cover diversified endpoints,*
  - *Neuro, Immunotox, MNT, TK*
- *Interim sacrifices at several age related landmarks.*
- *Identify and undertake etiology related bioassays at each landmark for the identified biomarkers*
  - *e.g. thyroid hormone assays*

Combinatorial Safety Evaluation Paradigm

- *Isolation of the tissues/ microsomes / cells to develop primary cells to be used for in vitro biomarker assays relevant to the age of sacrifice.*
  - *Bioassays with these primary cell lines as well as similar human immortalized cell lines to evaluate the responses to the test compound in respect of cytotoxicity, metabolism, Cyp assays, receptor binding assays, specific biomarkers... etc)*

Combinatorial Safety Evaluation Paradigm

- *in vitro* human cell based bioassays using immortalized human cell lines to establish human relevance.

- Comparison for relevance with the bioassay conducted using the primary cell lines of the isolated tissues

Combinatorial Safety Evaluation Paradigm

- Bioassays could be aimed at
  - *Thyroid relevance & evaluation of effects on Thyro-Pitutary axis*
  - *Metabolic and sex hormonal relevance*
  - *Pancreatic activity*
  - *Immuno-modulation*
  - *in vitro Mutagenicity studies (MNT & Chromosomal aberration) from the age relevant isolated primary cell lines of the test animal and corresponding human cells….*

Further reading

- *National Toxicology Program,*
  - An inter-agency program run by the United States Department of Health and Human Services to coordinate, evaluate, and report on toxicology within public agencies; https://ntp.niehs.nih.gov/
  - *Tox-21*
    - NTP Interagency Center for the Evaluation of Alternative Toxicological Methods Tox21 activities) https://ntp.niehs.nih.gov/pubhealth/evalatm/tox21-support/index.html
    - National Toxicology Program for the 21st Century: A Roadmap for the Future." https://ncats.nih.gov/tox21
- *EU-ToxRisk :*
  - An Integrated European 'Flagship' Programme Driving Mechanism-based Toxicity Testing and Risk Assessment for the 21st century
    - http://www.eu-toxrisk.eu/page/en/about-eu-toxrisk.php

Our Global presence…..

JRF GLOBAL

- **Business Development Hub Americas: Toronto & Philadelphia**

- **European Business Development Hub**

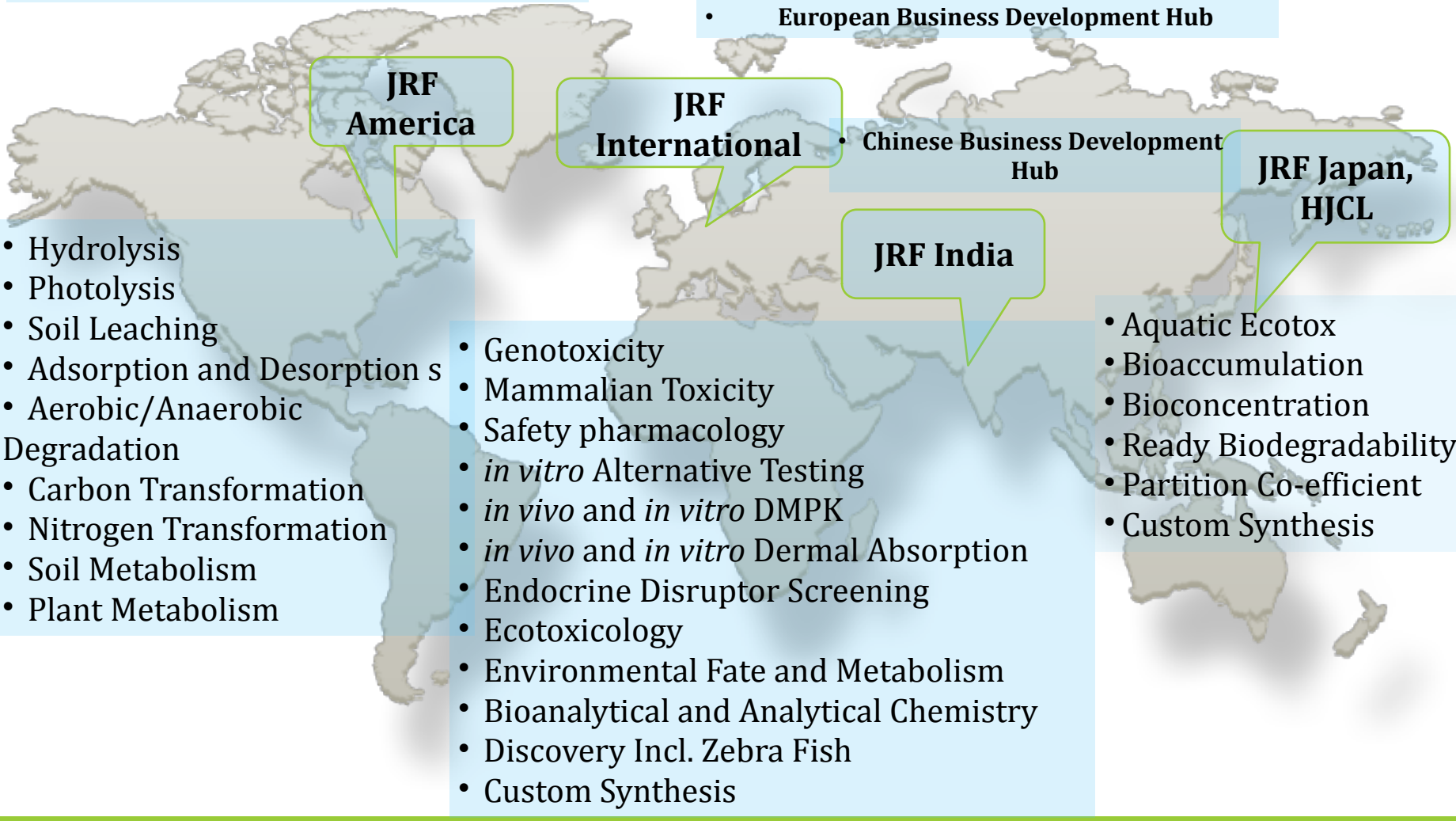
JRF America

JRF International

- **Chinese Business Development Hub**

JRF Japan, HJCL

JRF India



- Hydrolysis
- Photolysis
- Soil Leaching
- Adsorption and Desorption s
- Aerobic/Anaerobic Degradation
- Carbon Transformation
- Nitrogen Transformation
- Soil Metabolism
- Plant Metabolism

- Genotoxicity
- Mammalian Toxicity
- Safety pharmacology
- *in vitro* Alternative Testing
- *in vivo* and *in vitro* DMPK
- *in vivo* and *in vitro* Dermal Absorption
- Endocrine Disruptor Screening
- Ecotoxicology
- Environmental Fate and Metabolism
- Bioanalytical and Analytical Chemistry
- Discovery Incl. Zebra Fish
- Custom Synthesis

- Aquatic Ecotox
- Bioaccumulation
- Bioconcentration
- Ready Biodegradability
- Partition Co-efficient
- Custom Synthesis

Futuristic Combinatorial testing paradigm….

Any thoughts??

Think, have courage of conviction and go ahead……..

All our Dreams can come true, if we have the courage to pursue them……

Walt Disney

Thanks for your attention

ROSALIND FRANKLIN UNIVERSITY of MEDICINE AND SCIENCE

Dr. Abhay Deshpande

CEO

JRF GLOBAL

"INNOVATIONS IN BRIDGING THE *IN VIVO*/HUMAN EFFICACY AND TOXICOLOGY GAP TO ENHANCE SUCCESSFUL DRUG DEVELOPMENT"

JRF GLOBAL

Date: Tuesday, Sept. 19, 2017
Time: 4:30 – 5:30 pm
Location: Conference Room:
For: Researchers, Faculty, Industry, Entrepreneurs

Registration: (Limited Space)