# Innovations in New Drugs Development and Marketing

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# Presentation Profile

- About - **Centre For Advanced Research For Pre-clinical Toxicology.**
- Our stake holders.
- Role of stake holders.
- What are Pre-clinical Safety / Premarket Studies?
- Success stories of the centre .

# NATIONAL INSTITUTE OF NUTRITION (ICMR)

## CENTRE FOR ADVANCED RESEARCH FOR PRE-CLINICAL TOXICOLOGY (ESTD. 1998)

- DRUG TOXICOLOGY RESEARCH CENTER
- PATHOLOGY
- NATIONAL CENTRE FOR LABORATORY ANIMAL SCIENCES
- IMMUNOLOGY
- STATISTICS

**PCT Team**
Pharmacologist
Pathologist
Veterinary Pathologist
Biochemist
Trained Technical Staff

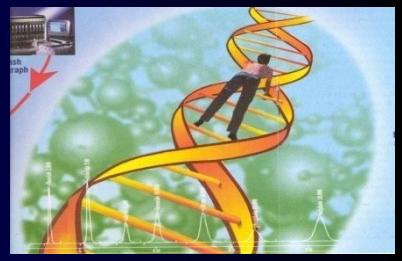
Team Work

**PCT Team**
Geneticist
Microbiologist
Animal Scientists
Statistician
Trained Technical Staff

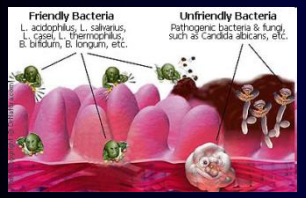
## Synthetic

## NUTRACEUTICALS

## Recombinants



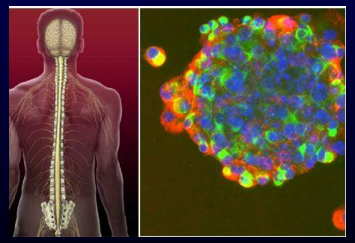
## PROBIOTICS



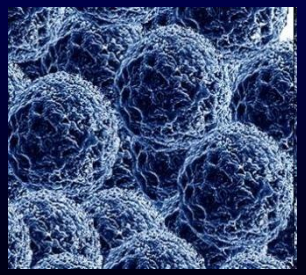

# DRUGS / CROPS OF THE MILLENNIUM

## GM / Foods

## STEM CELL THERAPY



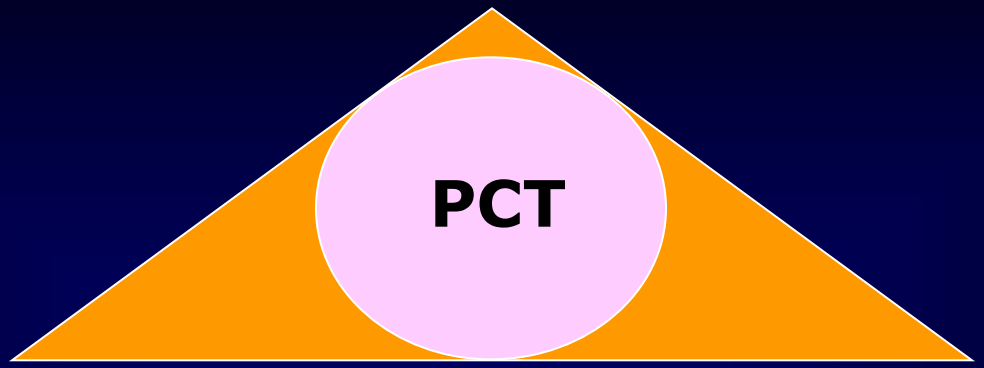
## NANO PARTICLES



## ? GM – Animals

# COLLABORATIONS ESTABLISHED

## NIN - Inter Institutional




### Govt / Public Institutes

- IISC, Bangalore
- IIL, Hyderabad
- AIIMS,New Delhi
- PGI, Chandigarh
- NDDB, Anand
- CCRAS, New Delhi
- DCGI, GoI
- CDRI, Luknow
- IICT, Hyderabad
- ANGRAU, Hyderabad
- University of Delhi
- DBT -BIPP
- DST
- ICAR (NAIP)

### Private Organization

- Virchow biotech
- Asian Herbex
- Cadila Pharma
- ISSAR Pharma.
- Stempeutics Pvt. Ltd.
- Vanjan Biopharma
- Bejosheetal Pvt. Ltd
- Mahyco Seeds
- JK Seeds
- Zenotech
- Crystalin research
- Sudhershan biotech

# PRODUCTS SCREENED FOR PRE-CLINICAL SAFETY EVALUATION

**Bio-Tech**

- Alpha interferon
- R-DNA anti-rabies vaccine (drv) & combination (crv)
- Hepatitis b vaccine (rhbvac)
- Japanese encephalitis vaccine, live attenuated (sa-14-14-02)
- Tetra valent
- HPV vaccine

**GM / Foods**

- Bt Cotton
- Bt Brinjal
- Bt Okra
- Bt Mustard

**Milk and oil products**

- Bio-Preservative Skimmed Milk Fermentate (SMF)
- Shea Olien
- DAG Oil

**Synthetic Molecules**

- Proprietary peptide molecule (anti-cancer)

**Traditional**

- Ayurvedic formulations- a,b,c,d,e (WHO Biennium Programme).
- Ayurvedic Bhasmas (herbo-mineral preparations)
- Preclinical Toxicity OF Chlorella Vulgaris E-25

# 9 Reasons why An Apple a Day Really Keeps the Doctor away ?

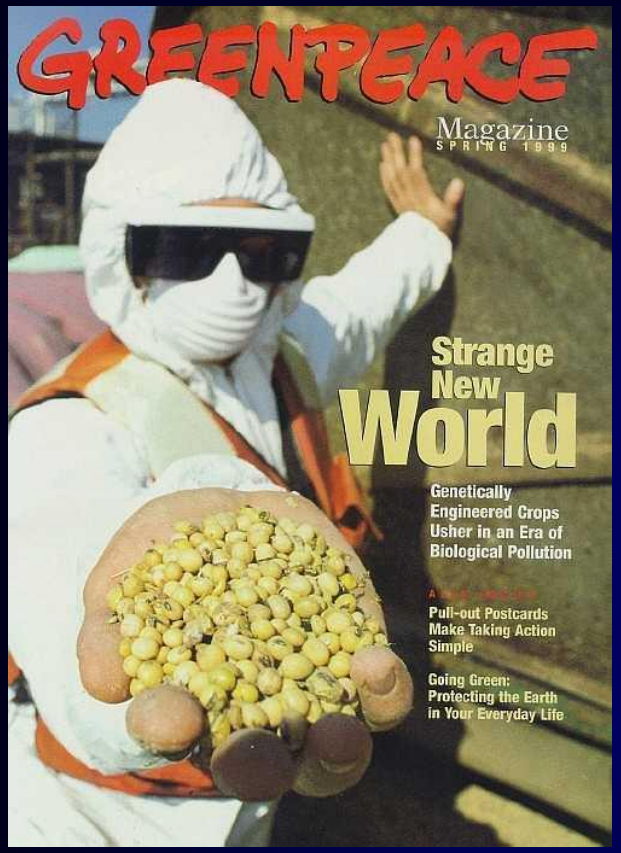
1-Apple contains Vitamin C, 2-Prevent Heart Diseases, 3-Low in calories, 4-Prevent Cancers, 5-Apples contain phenols, 6-Prevent tooth decay, 7-Protects your brain from brain disease, 8-Healthier Lungs, 9-They taste great!

**MYTH BUSTED**

**An Apple a day brings dentist closer ?**

**Eating regularly 4 times damages 2mm surface enamel of teeth**

# CAN WE FACE CHALLENGES ?



**YES !**

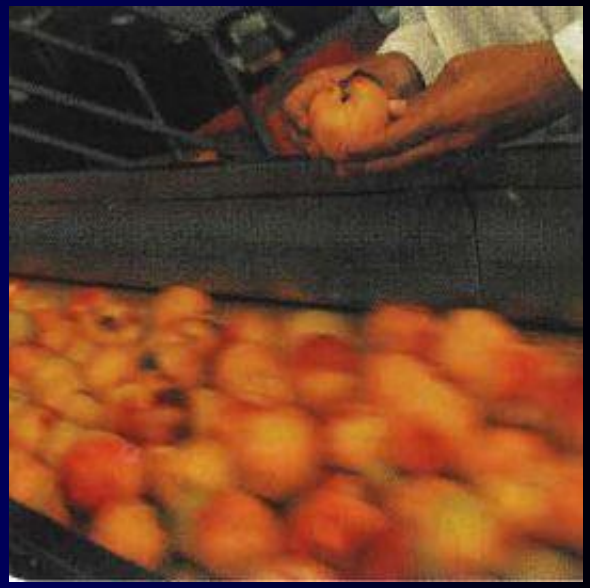
LET US PREPARE

IDENTIFY THE INTERVENTION STRATIGIES

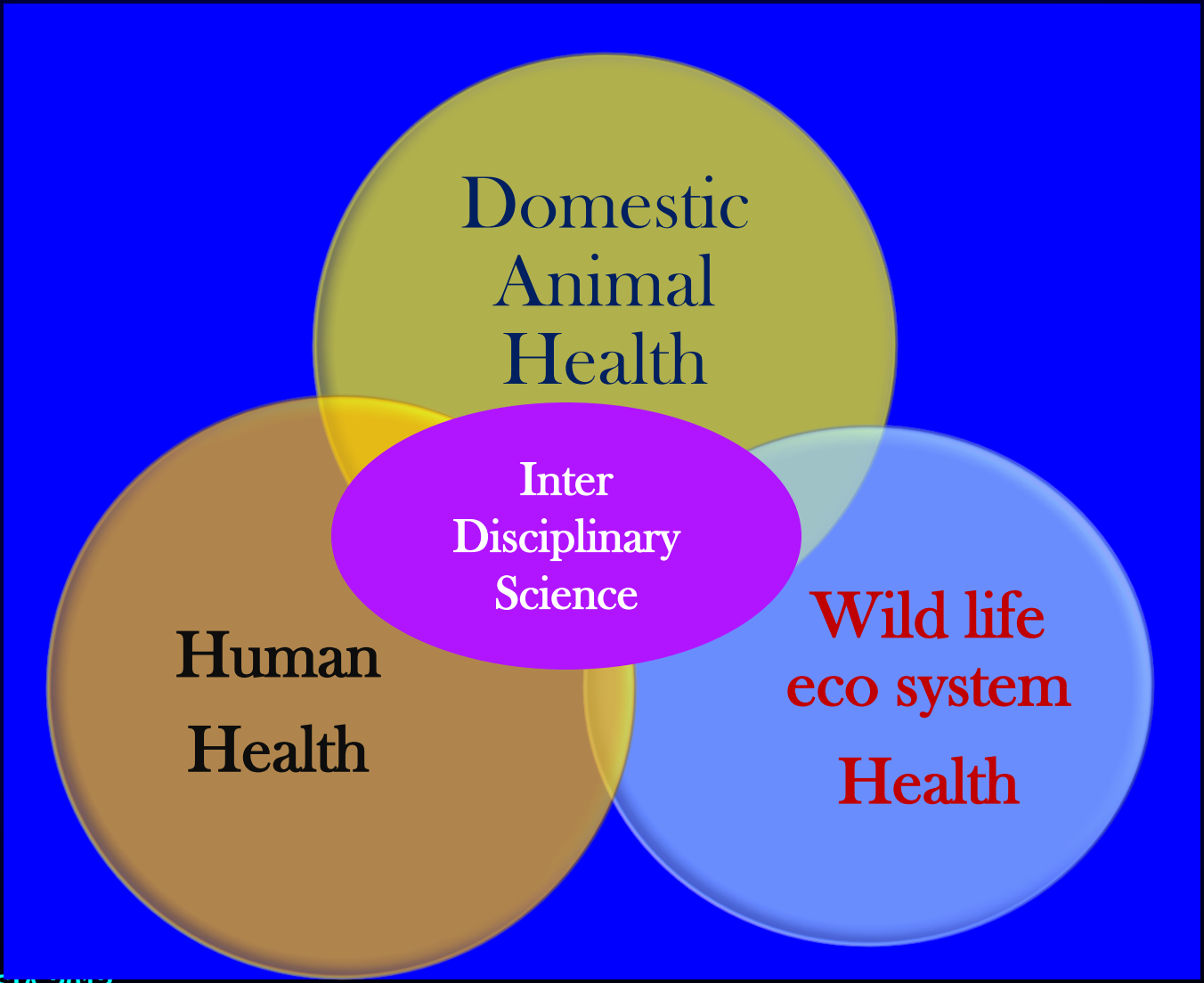
# Advancing Regulatory Science

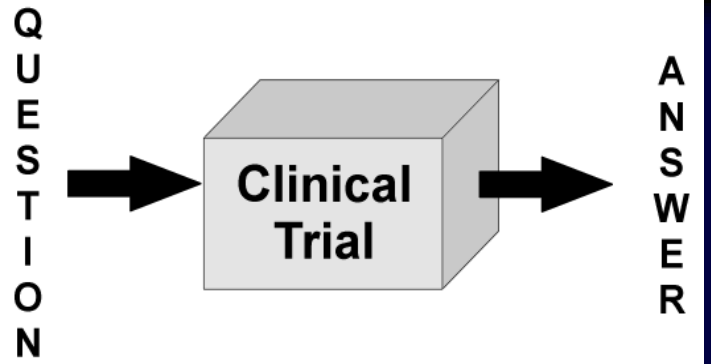
Margaret A. Hamburg is Commissioner of the U.S. Food and Drug Administration.

ENSURING THE SAFETY AND QUALITY OF FOOD AND MEDICAL PRODUCTS HAS NEVER BEEN MORE complicated. Societies around the world face increasingly complex challenges that require harnessing the best available science and technology on behalf of patients and consumers. This effort requires a strong field of regulatory science to develop new tools, standards, and approaches that efficiently and consistently assess the safety, efficacy, quality, and performance of products. Yet, despite being a critical component of the scientific enterprise, regulatory science has long been underappreciated and underfunded.



# Most Potential Inter Disciplinary Research






PHASE I

PHASE II

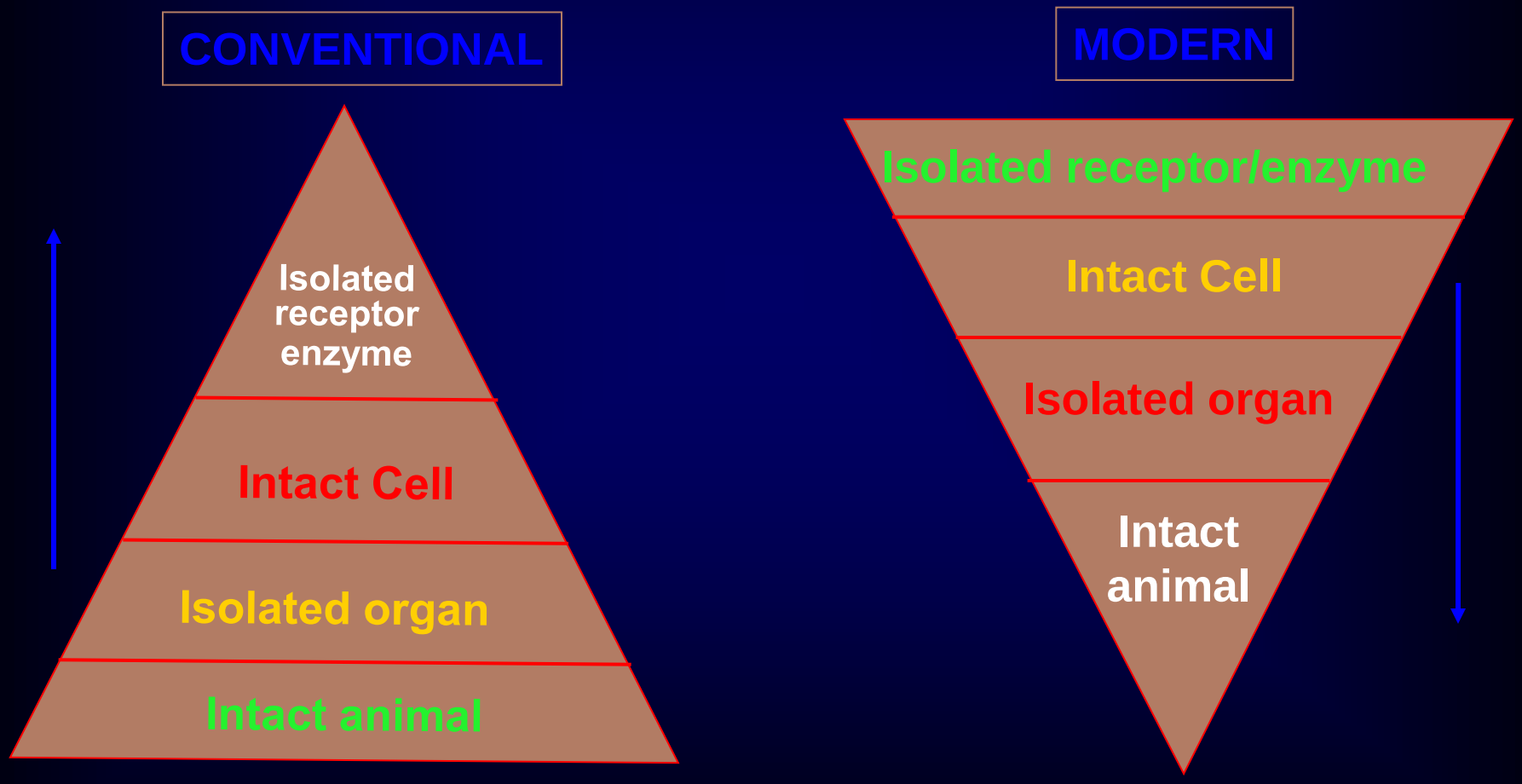
PHASE III

PHASE IV

# Prerequisites for a clinical trial

- Justification
- Supporting Preclinical data
- Investigator and study site
- Ethical Principles/ Declaration of Helsinki/ Nuremberg Code
- Regulatory requirements
- Monitoring mechanism

# PARADIGM SHIFT IN DRUG EVALUATION

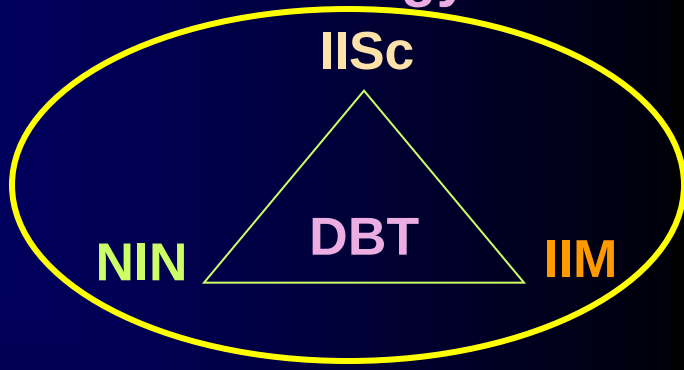


# CASE STUDY IN INDIAN LABORATORY - NIN: SAFETY EVALUATION OF r-DNA ANTI-RABIES VACCINE

## HISTORY & ORIGIN

**NTV:** Neural Tissue Vaccine (Banned all over the world)
- 35,000 ltrs. from 30,000 sheep's
- Production is painful process - Crude technology
- Major side effects

**TCV:** Tissue Culture Vaccine
- Expensive/Advance Technology

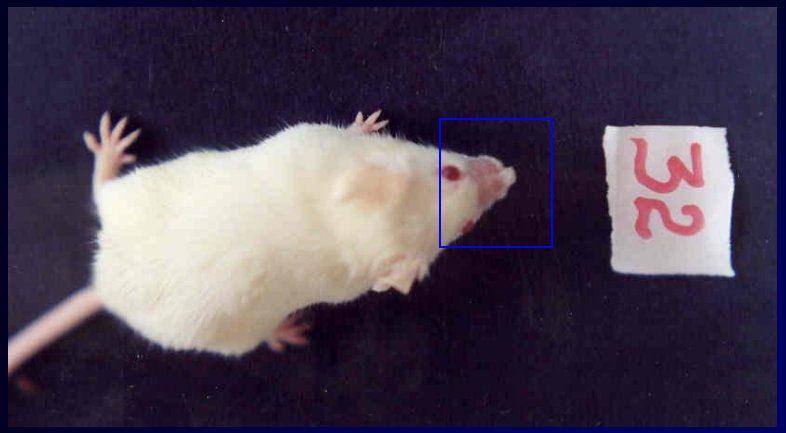



**Supreme Court :** Justice B.N.Kirpal Singh 15/02/2002
PIL 2/06/2001 - Ban production of NTV

*60,000 Cases/year - Local needs, indigenous technology*

*IISc Bangalore - DNA Anti Rabies Vaccine (DRV)*

# CHRONIC TOXICITY (Contd..)




EXPERIMENTAL

REFERENCE

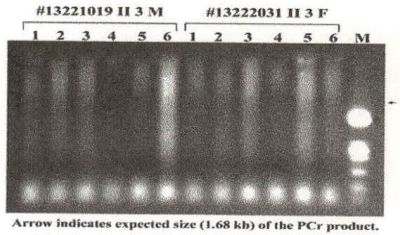
1. A female mouse may develop a fur-chewing vice and chew the hair off a cage mate or her litter. The hair over the nasal and orbital regions or the dorsal cervical area is most often barbered. The exposed skin is intact and normal in appearance. The only cure for barbering, if the client considers it a problem, is to remove the mouse that has not been barbered.

2. Alopecia often with accompanying epidermal thickening is one of the most common lesions seen in genetically engineered mice (GEM). Some times the causes of alopecia are frequently unknown, and may be related with the genotype of the mouse

3. Skin scrapings will have to be tested for mite infestation by microscopinc examination and fungal infestation by collecting the samples in Sabourauds Dextrose Agar.

# CHRONIC TOXICITY STUDY DNA-PRODUCT

## RESIDUAL DNA

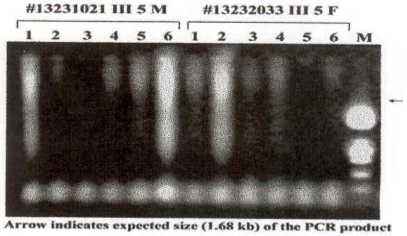



Arrow indicates expected size (1.68 kb) of the PCr product.

1: Liver 2: Heart 3: Kidney
4: Site of Injection 5:Spleen 6: Brain

Figure 1

Result: No PCR product is detectable in any of the tissues analyzed.

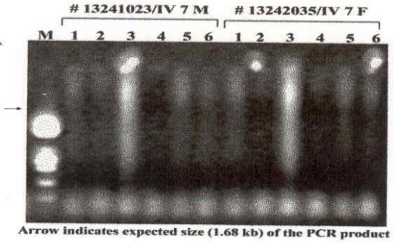



Arrow indicates expected size (1.68 kb) of the PCR product

1: Liver 2: Heart 3: Kidney
4: Site of Injection 5:Spleen 6: Brain

Figure 2

Result: No PCR product is detectable in any of the tissues analyzed.

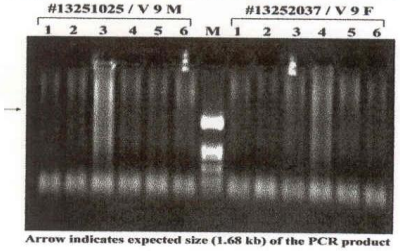



Arrow indicates expected size (1.68 kb) of the PCR product

1: Liver 2: Heart 3: Kidney
4: Site of Injection 5:Spleen 6: Brain

Figure 3

Result: No PCR product is detectable in any of the tissues analyzed.




Arrow indicates expected size (1.68 kb) of the PCR product

1: Liver 2: Heart 3: Kidney
4: Site of Injection 5:Spleen 6: Brain

Figure 4

Result: No PCR product is detectable in any of the tissues analyzed.

Arrow indicates expected size (1.68 kb) of the PCR product

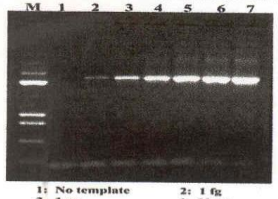
1: Liver 2: Heart 3: Kidney
4: Site of Injection 5:Spleen 6: Brain

Figure 5

Result: A PCR product of expected size was detectable in lane 4 of sample #13262039/VI 11F.

DETERMINATION OF SENSITIVITY OF PCR REACTION

PCR amplification of Rabies G protein cDNA from DNA Rabies vaccine plasmid (pCMVRab)




1: No template 2: 1 fg
3: 1 pg 4: 10 pg
5: 100 pg 6: 1 ng
7: 10 ng

Result: Upto 1femtogram of plasmid DNA can be detected by PCR

Figure 6

**The tissues of all animals were found to be negative for the presence of plasmid DNA.**

# CHRONIC TOXICITY STUDY (Contd..)

**Mice :** 33% (36) subject to haematology, biochemistry & histopathlogy 30th day

33% (36) subject to haematology, biochemistry & histopathlogy 60th day

34% (48) subject to haematology, biochemistry 90th day

34% (48) subject to haematology, biochemistry & histopathlogy 120th day

**Monkey:** All animals subject to haematological, biochemical, examination on 0, 14, 30, 90 and 120th day.

10 animals (1XDRV (1M + 1F), 1XCRV (1M + 1F), 2XDRV (1M+1F), 2XCRV (1M+1F) & 10XDRV (1M+1F)) subjected to gross necropsy, histopathology & immunopathology examination on 90th day of last exposure

**Mortality :** 3.3% (4 animals: 1 X CRV (2) & 2XCRV (2)) on 4th dose

**Results:** No significant observations in any parameters except hair loss

# STUDY RESULTS (Contd..)

## IMMUNOTOXICOLOGY

- **Immunopathology:** There were not difference in spleen weights no evidence of lymphoid, hyper or hypoplasia.

| | |
|---|---|
| Spleen | – Hyperplasia |
| Lymph nodes | - Reactive hyperplasia/Sinus Histiocytosis |
| Esophagus | - Lymphoid hyperplasia |
| Stomach | - Mucosal Lymphoid Aggregate |
| Small Intestine | - Lymphoid tissue in submucosa |
| Large Intestine | - Lymphoid tissue in submucosa |

- **Anti-DS-DNA/Anti nuclear antibodies:**
  There were not anti-ds-DNA antibodies and antinuclear antibodies in monkey serum samples exposed to test compound

# CHRONIC TOXICITY STUDY DNA-PRODUCT

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**Mortality :** 3.3% (4 animals: 1 X CRV (2) & 2XCRV (2)) on 4th dose

**Results:** No significant observations in any parameters except hair loss

# FINDINGS

- **Protocol violations :**

  Chronic toxicity test in New Zealand B/W Mice (10X\DRV)

  ? Required :

  No residual DNA detected except (1 femtogram of plasmid at site of injection of animal exposed to 10XDRV – 90 days) by PCR

  The serum samples showed negative for the anti-ds-DNA-antibodies & antinuclear antibodies in monkeys exposed various doses of DRV & CRV

- **Morbidity :**

  Hair loss in chronic toxicity studies in mice (14 nos) belonging to all the groups – not dose related,

- **Mortality :**

  3% (4 nos) mortality in mice 1CRV (2) & 2 CRV (2) after the 4$^{th}$ clinical exposure to test compound in chronic toxicity test – Due to handling

# REPORT ON PRECLINICAL TOXICITY OF r-DNA ANTI-RABIES VACCINE (DRV) AND COMBINATION RABIES VACCINE (CRV) TOXICITY STUDIES IN MONKEYS & MICE

**STUDY NOS. TOXI.NIN-BP-DRV/NHP/A/S/C/01/01**
**TOXI.NIN-BP-DRV/SAM/A/S/C/01/01**


**PRECLINICAL TOXICOLOGY UNIT**
**NATIONAL INSTITUTE OF NUTRITION**
**(Indian Council of Medical Research)**
**Jamai Osmania P.O.**
**HYDERABAD – 500 007, A.P.**
**INDIA**
**Phone No. +91 (40) 2700 8921, Fax No. +91 (40) 2701 9074**

# OUTDATED MYTH

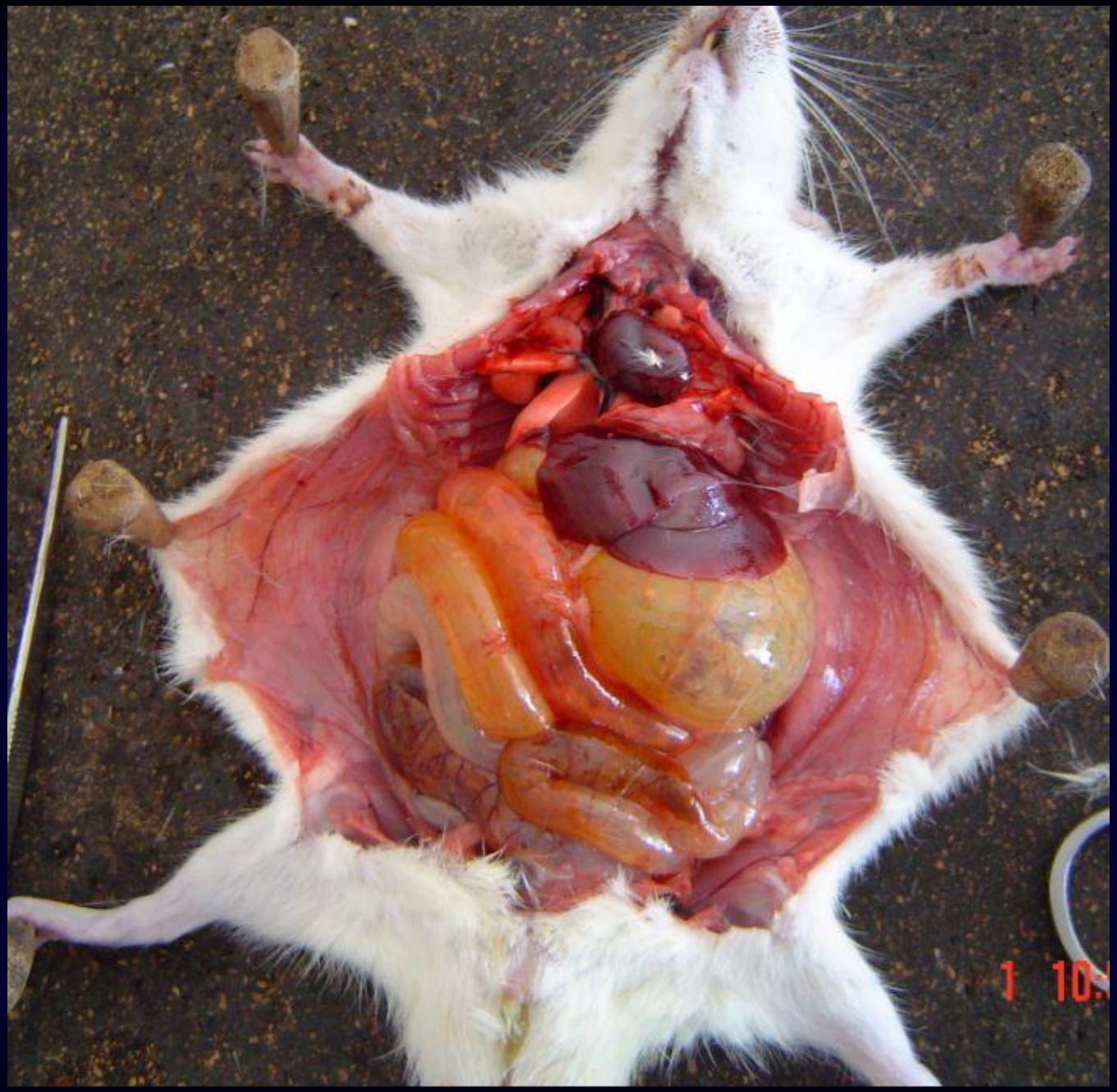
**Plants being Natural Products are safe ?**

**Increased Use**

**But Without Increased Awareness on Safety Concerns**

# Highlights of the study results

| S.No | Test Compound | Results |
|---|---|---|
| 1. | Formulation a | Pre terminal deaths (average 27%)<br>TD – 10%<br>AD – 30%<br>HD – 70%<br><br>Expt repeated<br>Similar observations<br>Autopsy suggested dilatation of stomach and intestine suggesting paralytic ileus |
| 2. | Formulation b | No abnormalities |
| 3. | Formulation c | Pre terminal deaths in male rats |
| 4. | Formulation d | No abnormalities |



# Comparative Guidelines Sub-Acute/Long Term Toxicity Test

| Details | FDA | ICH | WHO | ISM |
|---|---|---|---|---|
| Species | Rodent/Non-rodent<br>Rat/Dog | Rat/Dog/Rabbit | Rodent/<br>Non-rodent | Rats |
| Animal Nos. | 12-20X4/4-6X4 | 20X4/8X4 | 20X4/6X4 | 12X4 |
| Sex | Equal M/F | Equal M/F | Equal M/F | Equal M/F |
| Weight | Young adult | Adult | Adult | 150-200gms |
| Test compound exposure | Low<br>Intermediate<br>High | Therapeutic<br>NOAEL<br>Toxic dose | No effect<br>Intermediate<br>Toxic level | TH<br>THX2<br>THX5 |
| Duration | 2-6 weeks | 90 days | *please refer | 4 weeks |

| Clinical | | Experimental |
|---|---|---|
| * single/repeat < 7 days | : | 2-4 weeks |
| - do - 7-30 days | : | 4-12 weeks |
| 1-6 months | : | 3-6 months |
| > 6 months | : | 9-12 months |

M-Male
F-Female
R-Rodent
NR-Non-rodent

# SYNTHETIC PEPTIDE

## Acute, Sub Chronic Toxicity Study
## In
## Mice, Rats, Rabbits

# Pre-Clinical Toxicity of Proprietary Peptide Molecule (Genopep 1)

**Sponsor** : **xxx pharmaceuticals, Hyderabad**

**Test Centre** : **Centre for Advanced Research for Pre-clinical Toxicology, NIN (ICMR), Hyd**

**Test compound details** : **Synthetic peptide**

**23 Amino acids consisting of Alanine, Phenylalanine & Lysine**

**MW: 2775.42, formula – C144 H212 N32 O24**

**Intended Therapeutic efficacy** : **Potential with Anti – Tumor & Anti – Cancer activity**

**INTENDED DOSE SCHEDULE (CLINICAL)** **(Rational – Urologic Oncology (2001) 6; 97-102)**

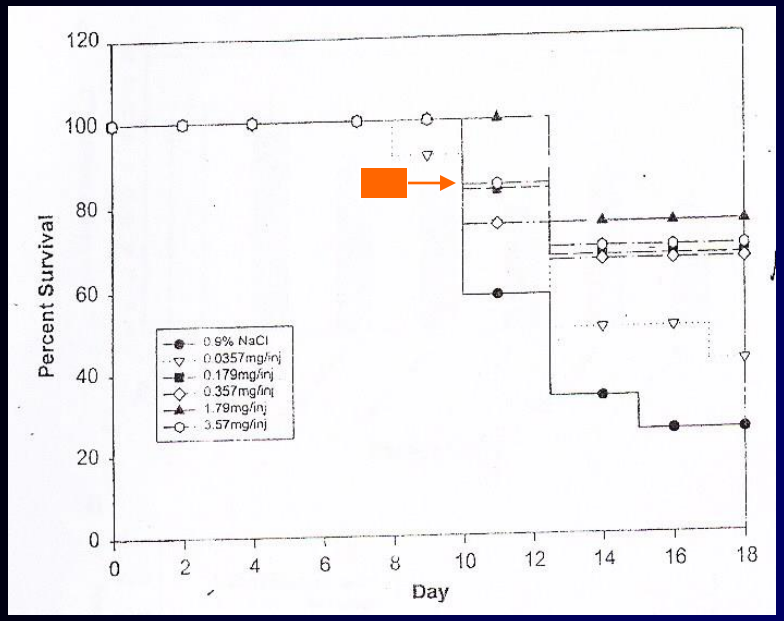
**Dose Human / Kg** : **0.143 mg/Kg**
**Dosage form** : **Injectable**
**Route of administration** : **Infusion / Intravenous / Intramuscular**
**Duration** :

| | |
|---|---|
| I.V | 5 days a week for two weeks |
| S.C | 5 days a week for four weeks |

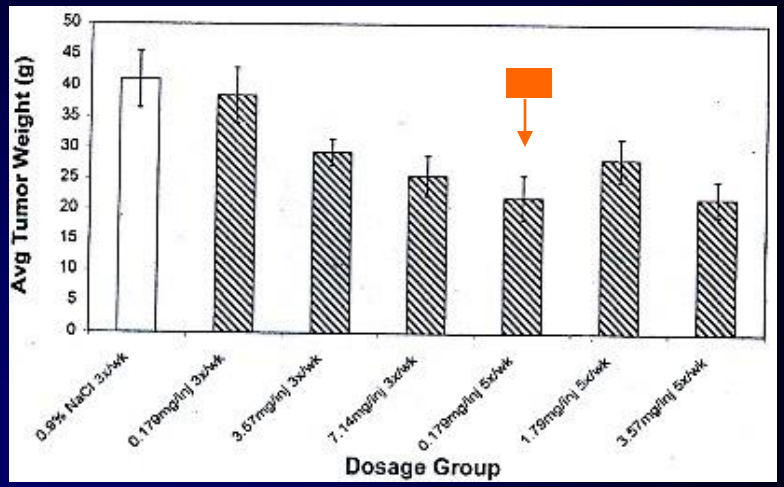
# TEST PROCEDURES

| S. No | Test Details | Species | Dose levels | Dosage schedule | | |
|---|---|---|---|---|---|---|
| | | | | Strength mg/kg | Route | Exposure / Duration |
| 1 | Acute | Mice (10) | 10XTD | 2.5 / 13 | SC / IV | Single exposure (14days) |
| | | Rats (10) | | 1.8 / 9 | | |
| 2 | Sub -acute | Rats (40) | TD | 0.9 | SC | 5 times in a week (28days) |
| | | | AD (5XTD) | 4.5 | | |
| | | | HD (10XTD) | 9.0 | | |
| | | Rats (48) | TD | 0.9 | IV | 5 times in a week - 2 weeks (28days) |
| | | | AD (2XTD) | 1.8 | | |
| | | | HD (3XTD) | 2.7 | | |
| | | Rabbits (24) | TD | 0.46 | SC | 5 times in a week (28days) |
| | | | AD (5XTD) | 2.33 | | |
| | | | HD (10XTD) | 4.65 | | |
| | | Rabbits (32) | TD | 0.46 | IV | 5 times in a week - 2 weeks (28days) |
| | | | AD (2XTD) | 0.93 | | |
| | | | HD (3XTD) | 1.39 | | |
| 3 | Long term | Rats (40) | TD | 0.9 | SC | 5 times in a week – 4 weeks (90days) |
| | | | AD (5XTD) | 4.5 | | |
| | | | HD (10XTD) | 9.0 | | |
| | | Rabbits (40) | TD | 0.46 | SC | |
| | | | AD (5XTD) | 2.33 | | |
| | | | HD (10XTD) | 4.65 | | |
| | Maximum TD@ | Dog (2) | 2XTD-10XTD | 0.5 – 2.6 | IV | 14 - 28days |

# RATIONALE FOR SELECTING THE DOSE




Survival of Animals with meta static prostrate cancer




Inhibition of tumor growth with metastatic prostrate cancer

1. Survival rate of the treatment group received 0.179mg significantly increased 70-75% in animals challenged with large number of aggressive and Matastatic Mat-Ly-Lu (MLL) cancer cell lines.
2. The intraperitonial administration of peptide (0.179mg) 5 times / week significantly enhanced anti tumor activity.
3. With higher dosage the toxicity was exhibited at the site of injection which indicated peritonitis.
4. 0.179mg for injection significantly (50%) anti-tumor activity without any toxicity.



Arlotti, etal (2001), Urologic Oncology 6; 97-

# Reaction at site of injection of Test Compound )

**Observation after final (10th) exposure:**

**VC Group**

**TD Group**

**AD Group**

**HD Group**

# Reaction at site of injection of Test Compound (contd..)

**Observation of Rabbits after final (10th) Exposure: :**

VC Group

TD Group

AD Group

HD Group

# STUDY IMPRESSION

| S.No | Species | Dosage schedule | | | Observation |
|---|---|---|---|---|---|
| | | Route | Strength (mg/kg) | Duration | |
| 1 | Mice | SC | 13.0(10XTD) | Single | NOAEL – Subcutaneous (10XTD) 9mg/kg in rats & 4.65mg/kg in Rabbits |
| 2 | Rat | | 9.0 (10XTD) | 5/day - 4wk | |
| 3 | Rabbit | | 4.65(10XTD) | | |
| 4 | Mice | IV | 13.0 (10XTD) | Single | NOAEL – Intravenous (2XTD) 1.8mg/kg in rats & 0.93mg/kg in Rabbits |
| 5 | Rat | | 2.7 (3XTD) | 5/day - 2wk | |
| 6 | Rabbit | | 1.4 (3XTD) | | |
| 7 | Dog | IV | 2.6 (10XTD) | Single dose esculation from 2XTD | MTD – Intravenous (7.5XTD) 2.6mg/kg in dogs |

| Intended Human Dose | | | |
|---|---|---|---|
| Clinical Dose | 0.143 (1XTD) | 5/day –2wk | Intended Clinical Therapeutic Dose – IV & SC - 0.143mg/kg<br>Maximum Tolerated Dose level – IV<br>0.286mg/kg - based on Rats and Rabbits<br>Maximum Tolerated Dose level – SC<br>1.43mg/kg - based on Rats and Rabbits |

# PRE-CLINICAL TOXICITY EVALUATION OF EX-VIVO CULTURED HUMAN ADULT MESENCHYMAL STEM CELLS (MSC'S).

FORMULATIONS NAME :Ex-vivo cultured Human adult Mesenchymal Stem Cells (MSC's). **Supplied in cryobags**

| | |
|---|---|
| Mesenchymal Stem Cells | 200million |
| Human Serum Albumin (HSA) | 0.75ml (5%) / Plasmalyte A - 12.75ml (85%) |
| Plasmalyte A | 12.75ml (85%) |
| DMSO | 1.5ml (10%) |

| | |
|---|---|
| Therapeutic efficacy | Acute Myocardial Infarction (IV) & Critical Limb Ischemia (IM) |
| Dose (Clinical) | |
| • Dose strength | 2 x $10^6$ cells per kg body weight |
| • Dosage form | Parenteral |
| • Route of administration | Intravenous & Intramuscular |
| Sponsor: | Stempeutics Research Pvt. Ltd, Manipal, Bangalore. |
| Study Center | Centre for Advance Research for Pre-clinical Toxicology, FDTRC, NIN, (ICMR), Hyderabad |

# PRE-CLINICAL TOXICITY EVALUATION OF ANTI HPV (HUMAN PAPILLOMA VIRUS) Pg No.72

**Sponsor : Indian Immunologicals Limited**

## TEST COMPOUND DETAILS

a) **Name of the Formulation** : Anti-HPV Oral Vaccine (Recombinant Salmonella typhi strain expressing HPV18 L1 and HPV16 L1 VLPs)

b) **Therapeutic efficacy** : Prophylactic Vaccine to prevent cervical infection by HPV16 & 18(70% of these infections leads to cervical cancer

c) **Dose (Clinical)**

i) **Dose strength** : $2X10^9$ CFU each recombinant strain of HPV16and HPV18L1 expressing Salmonella typhi

| Dose | Day |
|---|---|
| First dose | 1st day |
| Second dose | 3rd day |
| Third day (Booster dose) | 5th day |

ii) **Dosage form** : Freeze dried powder

iv) **Route of administration** : Oral

CSDCO-OPT-BR3

# Lessons –TGNI421

**MONOCLONAL ANTIBODY— anticancer drug**

**Animal Experiment** | **? Pre-clinical Safety**

↓

**PHASE-I CLINICAL**

**UTTERLY DREADFUL TRIALS FOR TRAGEDY**

**Six men Northwick Hospital with 2 in coma**

**? Can healthy volunteer for study**

**? still speculative-**

- **POTENTIAL DOSING ERROR**
- **PRODUCT MANUFACTURING DEFECT**
- **IMMUNE REACTION**
- **INFLAMMATORY CYTOKINES**

**Source: Prescriber 2006;17:9**

# ? Preclinical predictors of Clinical Safety OR Opportunities For Improvement

**150-COMPOUNDS DATA PREDICTS**

| | |
|---|---|
| RODENT TOXICOLOGY TOXICITIES | – 43%- HUMAN |
| NON-RODENT TOXICOLOGY TOXICITIES | – 63%- HUMAN |
| TOGETHER TOXICITIES | – 71%- HUMAN |

Source: CPT, 2007, 82, 211-214

# Infrastructure

Metabolic cages for Mice

Pyrometer

Heavy duty Sliding Microtome

Metabolic cages for rabbits

& guinea pigs

Hematology Analyzer

Grip Strength Mete

NIN-BIOASIA-2013

IVC Cage rack model

Plethysmograph (16B)

High resolution research microscope with digital camera and image analysis system

# Infrastructure for evaluating the various components

Polygraph (Bio-pac)

TOBEC

ROTA ROD

Polycarbonate Cages

**Antihypertensives**
**Appetite stimulants**
**Nerve coordination**
**Analgesics /anti-inflammatory & anti-pyretic**
**Anti-obesity**
**Anti-asthamatic**

Autopsy Facility

Biochemical Analyser

Event Counter

Fluorescent Microscopy

Tissue Stainer

Oxy-max

Advanced Tissue Stainer

Recent proposal to DST – Strength other facilities

# Herbals and nutraceuticals for anti-atherosclerotic activity

APPROCH

Extraction of selected herbals and nutraceuticals

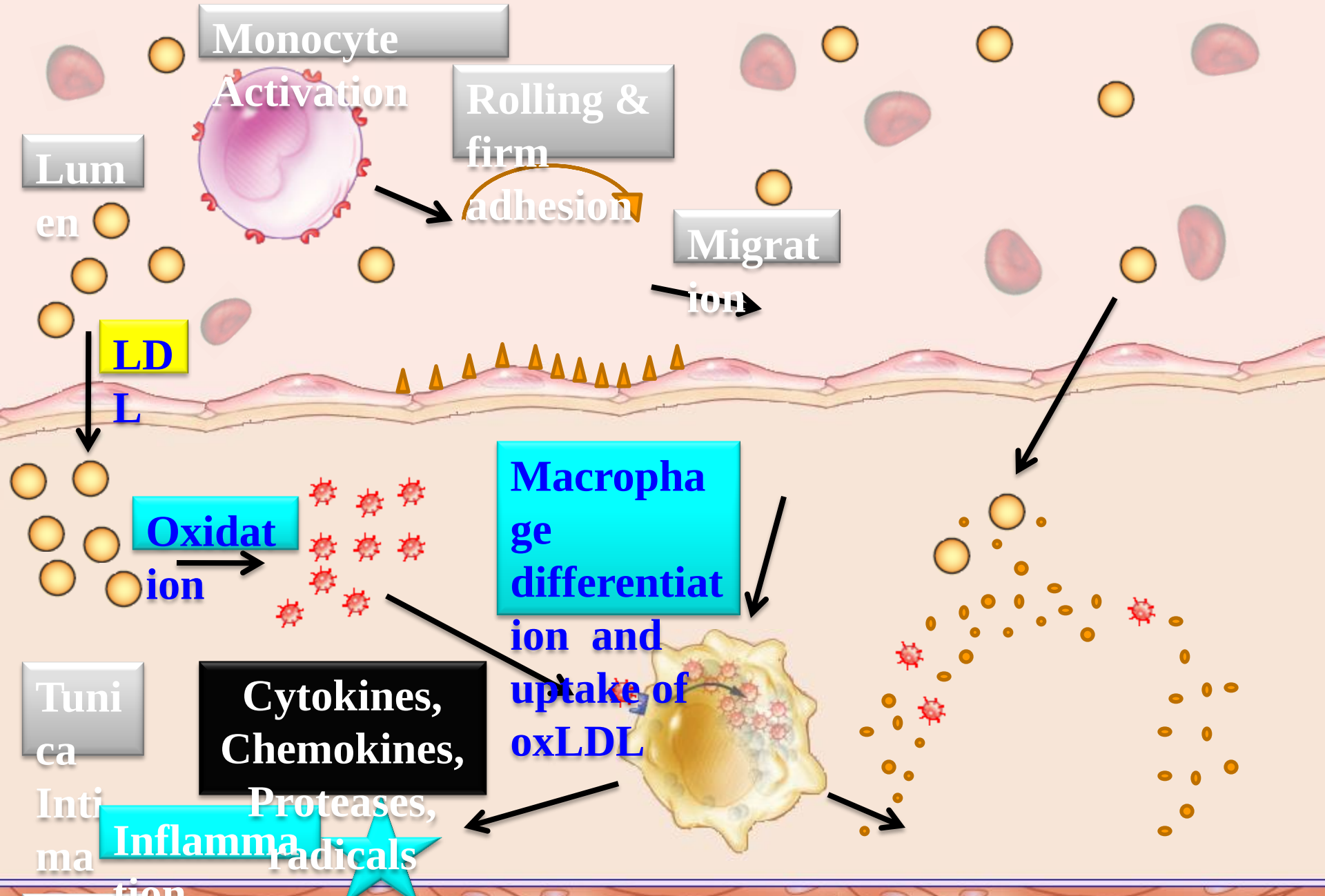
Screening of in-vitro biological activity

- Antioxidant
- Anti-foam cell formation
- Anti-inflammatory

Qualitative assessments of potential herbals / nutraceuticals by LCMS, NMR, MS-MS

Effect of herbal and nutraceuticals products on Monocyte adhesion

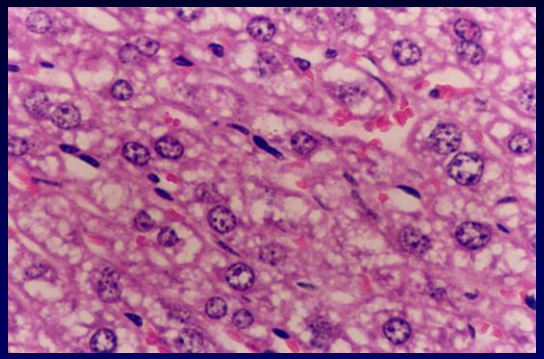
In-vivo anti-atherosclerotic activity in animal model



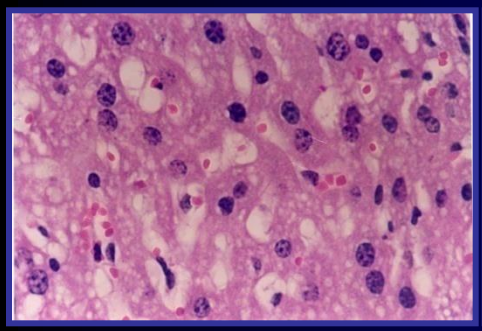

# Mechanism of atherosclerosis

# HISTOLOGICAL EVIDENCE OF % OF NORMAL CELLS WITH TIME AND DOSE

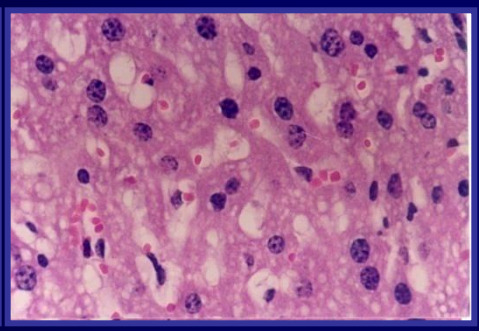
Fresh liver



EXPLANTS WITHOUT TEST COMPOUND



2HRS



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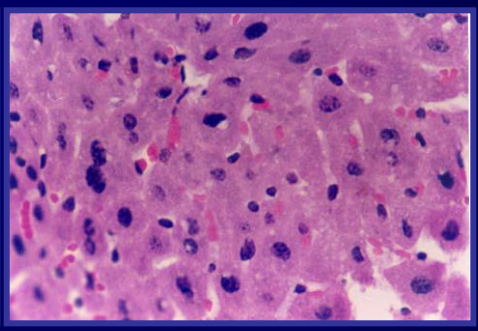
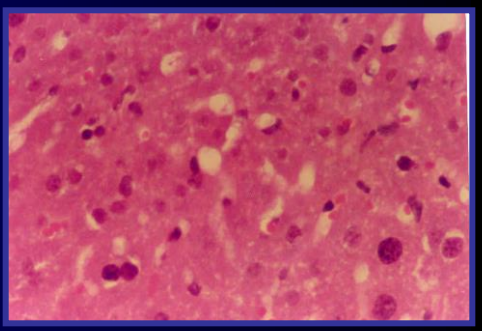
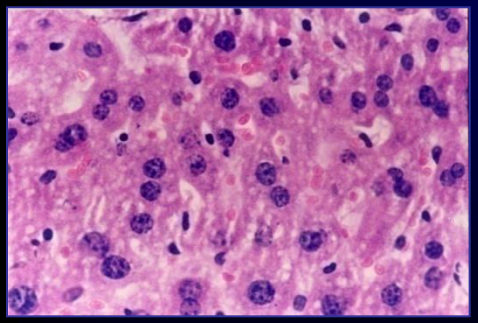
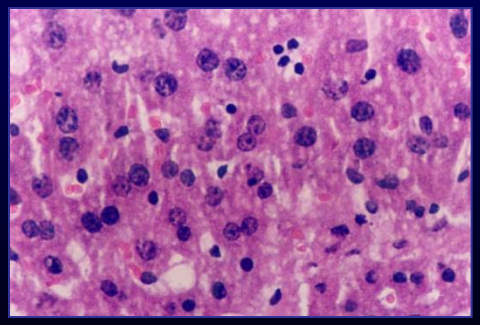


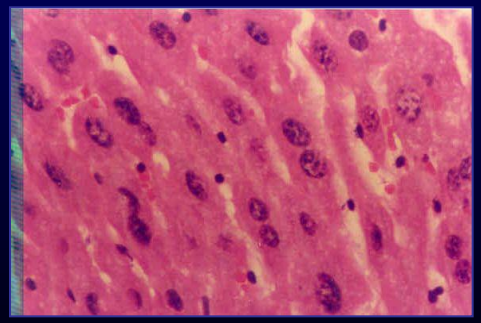
8HRS

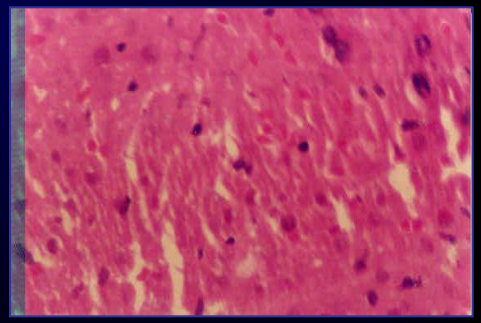


24HRS





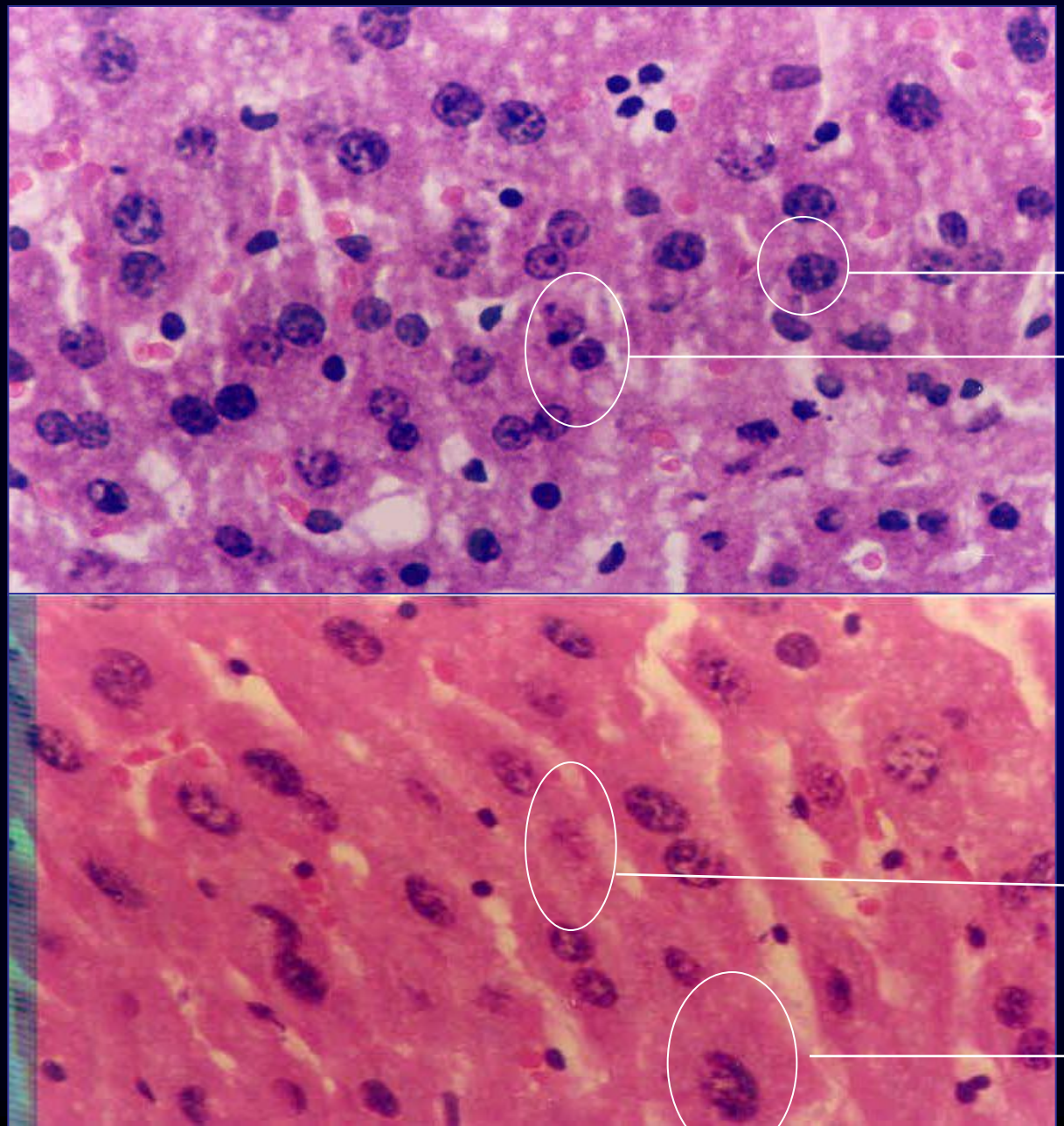




EXPLANTS WITH TEST COMPOUND 4308 (2ug/ml)

# EX-VIVO

## CELL COUNT



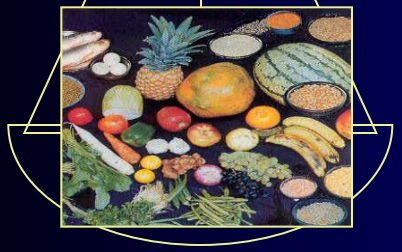

Total 500 cells were counted per slide and the % of normal cells were calculated

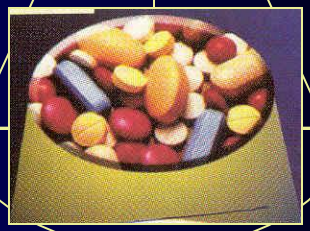
| S.No | Test Details |
|---|---|
| 1 | Pre-clinical Safety studies (Acute, Sub-chronic, Multi-generation studies as per regulatory and non regulatory requirement) |
| 2 | Determining Efficacy potential for following disorders |
| 2.1 | In-vitro anti-oxidant profile |
| 2.2 | In-silico evaluation |
| 2.3 | In-vivo evaluation for following disorders |
| 2.3.1 | Anti-inflammatory potential |
| 2.3.2 | Anti-Atherosclerotic activity |
| 2.3.3 | Anti-Hyperglycemic agents |
| 2.3.4 | Anti-obesity agents |
| 2.3.5 | Immuno-modulators |
| 2.3.6 | Anti-Inflammatory Bowel disorders |
| 3 | Determination of fungal toxins and afflotoxins Heavy metals in herbals |

# THE UNBEATABLES

## THANK YOU

*HEALTH CANNOT BE BUILT AT PHARMACY COUNTER*





ECONOMICAL, FRESH, TASTY, BETTER ABSORBED AND RETAINED. AVAILABLE IN NATURAL FORM AND RICH IN FIBER.

EXPENSIVE, SYNTHETIC, HAZARDOUS IF TAKEN IMPROPERLY / IN EXCESS PRODUCE UNWANTED SIDE EFFECTS.

**Concept (1994); Dinesh Kumar &Kamla Krishnaswamy**

Collaborations only can
Provide the Excellent
Results