Phase I trial of systemic administration of Edmonston strain of measles virus, genetically engineered to express NIS, with or without cyclophosphamide, in patients with recurrent or refractory multiple myeloma

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NCI RAID Program

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NCI RAID Program
Multiple myeloma

Plasma cell malignancy
Paraproteinaemia
Bone destruction
Hypogammaglobulinaemia

Currently incurable
11,000 deaths per year (USA)
Disseminated from outset
Survival ~ 4yrs
Virotherapy

Viruses destroy tissue

Maybe this destructive power could be harnessed for cancer therapy
Measles as an oncolytic agent

Bluming and Ziegler (1971) Lancet ii, 105-106

- Efficiently infects and kills human myeloma cells (via CD46)
- Selectively kills myeloma cells, spares normal cells
- Has potent antitumor activity against xenograft models of human multiple myeloma
- Can be engineered to express additional genes; recombinants are extremely stable
Edmonston Vaccine Lineage
(Rota et al. 1994, Virus Res., 31:317)

Edmonston
  HK/24
  HK/24
  HA/28
  HA/28

Edmonston-Enders
  HK/7
  Vero/6
  HA/12
  SK (33°C)/17*
  CEF (33°C)/22*

AIK-C

Edmonston Seed A
  HA/28
  CE (am)/22
  DK/15
  WI-38/19*

Zagreb

Edmonston Seed B

CEF(36°C)/3
CEF(36°C)/8
CEF(32°C)/40
CEF(32°C)/85
CEF(36°C)/22
CEF(36°C)/5
CEF(33°C)/22*
CEF (32°C)/85

Schwarz

Edmonston B
  Rubeovax

Moraten

MV-SPUD

Infectious clone

(Radecke et al., 1995 EMBO J, V14, p5773)
Measles virus cytopathic effect (cell fusion)

Viable syncytium

Non viable syncytium

Entry

Fusion

Apoptosis
Fusogenic proteins: measles F and H

H binds to CD46 or SLAM
F triggers fusion

SLAM is expressed only on activated immune cells.
CD46 is ubiquitous
CD46 is overexpressed on human myeloma cells.....
High CD46 expression in multiple myeloma

- Expressed at higher density on myeloma cells
- NOT myeloma specific
- Therapy should specifically attack high density

Unsorted bone marrow aspirated from patients with multiple myeloma
Syncytial Index

Cell Killing

Syncytial index

Cell viability

Syncytial Index

Cell Killing
MV-Edm oncolytic activity in myeloma

Measles virotherapy for myeloma: Problems with MV-Edm.

1. Inability to monitor spread

2. Anti-measles antibodies may block vascular delivery

3. Anti-measles cytotoxic T lymphocytes may prevent intratumoral spread
Recombinant measles viruses

MV-CEA: IP
ovarian cancer

MV-NIS: IV
multiple myeloma
MV-CEA Clinical Protocol

• Advanced ovarian cancer

• IP administration of MV-CEA in 500 ml saline

• Repeated every four weeks x 6

• Dose escalation (10^3 to 10^8)

• CEA monitoring to guide dose escalation

• No manufacturing problems

• Six patients treated (three at 10^3, three at 10^4)

• No dose-limiting toxicities

• Transient viremia in two patients

• No CEA elevations yet......
The thyroidal sodium iodide symporter (NIS)

Radioiodine

I-123  gamma  0.5 days  
I-124  positron  4 days  
I-125  gamma  60 days  
I-131  beta + gamma  8 days  
Tc99m  gamma  0.2 days
Imaging virus spread (MV-NIS)

I-123 or I-124 ip

NIS gene

Gamma camera

SPECT/CT

QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.

PET/CT

QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.

MV-NIS iv

NIS protein

I-123 or I-124 ip

QuickTime™ and a TIFF (Uncompressed) decompressor are needed to see this picture.
MV-NIS (intravenous) is a potent anti-myeloma agent

KAS6/1 model

- UV-inactivated
- $10^4$ MV-NIS
- $10^5$ MV-NIS
- $10^6$ MV-NIS
- $10^7$ MV-NIS

Tumor volume (mm$^3$) vs. Time After Therapy (days)
Measles virotherapy for myeloma: Problems with MV-Edm.

1. Inability to monitor spread

2. Anti-measles antibodies may block vascular delivery

3. Anti-measles cytotoxic T lymphocytes may prevent intratumoral spread
Low Anti-Measles Antibody Titers in Myeloma Patients

- Normal
- MGUS
- MM
- MM (SCT)
Cyclophosphamide suppresses immune response to MV

IFNAR Ko CD46 Ge mice

IP injection MV-CEA

+- cyclophosphamide 125 mg/kg

Peng et al, Nature Medicine 2002, 8, 527-531
The Status of Myeloma Therapy

- Progress past decade….
  - Transplantation, thalidomide, lenilidomide, bortezomib
- But patients dying—no cure in sight
  - 11,000 deaths per year; 15,000 new cases
- Innovative therapies are required
No Survival Plateau

- Single versus Double Transplant

- Median EFS < 3 years

Attal NEJM 349:2495-02
# Phase I Trial

## Step 1: MV-NIS alone

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Route</th>
<th>Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>MV-NIS</td>
<td>$10^6$ to $10^9$</td>
<td>30 min I.V.</td>
<td>1</td>
</tr>
</tbody>
</table>

*TCID$_{50}$*

## Step 2: MV-NIS + Cyclophosphamide

<table>
<thead>
<tr>
<th>Agent</th>
<th>Dose</th>
<th>Route</th>
<th>Day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclo</td>
<td>10 mg/kg</td>
<td>I.V.</td>
<td>-2</td>
</tr>
<tr>
<td>MV-NIS</td>
<td>$MTD/100$ to $81 \times MTD/100$</td>
<td>30 min I.V.</td>
<td>1</td>
</tr>
</tbody>
</table>
Trial Schema

CTX  MV-NIS

Day -4 -2 1 3 8 15 20 28 42 Q 3 mo

Cyclophosphamide
MV-NIS
CBC, chemistry, coagulation
Viral levels, Blood, sputum & urine

KEY
- Free light chain
- 123-I gamma camera imaging
- Bone marrow aspirate/biopsy
- Anti-MV antibody and T cell subsets
Potential toxicity & complications

1. Cytomel: tachycardia, tremor

2. 123-I: none

3. MV-NIS
   a. Infusion reaction
   b. Measles-like illness
   c. Virus transmission

4. Cyclophosphamide
   a. Immunosuppression: worsening of 2b-c?

Screen for symptomatic CAD and arrhythmia. Reduce dose to 25 mcg bid
Potential toxicities-MV-NIS

Infusion reactions

- **Allergic** → acetaminophen & benadryl
- **Rigors** → meperidine hydrochloride
- **Anaphylaxis** → cessation of infusion; fluids, benadryl, methylprednisone and epinephrine
Potential complications-MV-NIS

Measles-like illness

Fever, rash, coryza, transient immune suppression ± otitis media, pneumonia, encephalitis

Possible since myeloma patients are immunocompromised, but should be self-limited because….
Potential complications-MV-NIS

Measles-like illness

.... because measles vaccine....

- .....strains are extremely safe after billions of doses administered

- .....is recommended for
  - HIV-infected children
  - Immunosuppressed patients following HSCT

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- We routinely give MMR post HSCT to MM patients
Potential complications-MV-NIS
Measles-like illness

Contingency plan

- Measles immunoglobulin
- Ribavirin

Potential complications-MV-NIS

Safety of Starting Dose?

- $10^6 \text{TCID}_{50}$
  - HIV$^+$ & HIV$^-$ infants
  - Edmonston IV to monkeys
  - Upcoming primate studies

- **Efficacy**: Lowest effective in mice:
  - $\text{TCID}_{50} 10^5 \sim 5 \times 10^6$/kg; Trial starting dose:
  - $10^6 \sim 1.4 \times 10^4$/kg in 70 kg human
Potential toxicities-MV-NIS

Transmission to contacts?

- **RNA virus** – *mutation possible, but...*

- **Vaccine strains of measles** never reported to revert and/or to be transmitted

- **Vast majority of U.S. citizens vaccinated for measles**
Possible pharmacology/toxicology models

1. **CD46 transgenic IFNaRko mice** (+/- SCID)

2. CD46 transgenic pigs

3. Cotton rats

4. **New world (eg squirrel) monkeys**
   Old world (eg rhesus) monkeys

3. +/- cyclophosphamid

**Issues:**

- CD46 expression
- SLAM expression
- intracellular restriction
MV-NIS biodistribution in CD46tg, IFNARko mice (preliminary)

Group 1: $10^5$ TCID50 MV-NIS
Group 2: $10^7$ TCID50 MV-NIS
Group 3: UV-inactivated MV-NIS
Group 4: 125 mg/kg cyclophosphamide plus $10^7$ TCID50 MV-NIS

Studies performed day 90 after MV-NIS administration were negative for all organs, all groups.
Potential complications-MV-NIS

Measles-like illness, virus persistence or transmission?

- Primate Toxicology
  (12 Squirrel Monkeys)

- Primate studies with scheduled sacrifice
  - Two monkeys from each group: day 29
  - Remaining animals: day 91

<table>
<thead>
<tr>
<th>Group</th>
<th>MV-NIS (TCID\textsubscript{50})</th>
<th>CTX (mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>II</td>
<td>0</td>
<td>31</td>
</tr>
<tr>
<td>III</td>
<td>$10^8$</td>
<td>0</td>
</tr>
<tr>
<td>IV</td>
<td>$10^8$</td>
<td>31</td>
</tr>
</tbody>
</table>
Squirrel Monkey Schema

**KEY**
- **CTX**
- **MV-NIS**
- **Sacrifice-necroscopy**
- **CBC, chemistry, coagulation**

- **Green Arrow**: Cytokine measurement
- **Red Arrow**: Anti-MV antibody measurement
- **Blue Arrow**: Viral levels, sputum & urine (PCR)
- **Purple Arrow**: Viral levels, blood (PCR)
Monkey Necropsy Samples (41)

- Kidneys, bladder, adrenals
- Bone, femoral head with articular surface
- BM: sternum and rib
- Eyes, brain, pituitary, spinal cord, sciatic nerve
- Stomach, esophagus, duodenum, jejunum, ileum, cecum, colon
- Gonads, prostate, epididymides
- Liver, spleen, gall bladder, pancreas
- Gross lesions
- Heart, Aorta
- Lip, salivary gland, tongue, tonsils
- Lungs, trachea
- LN: bronchial, mandibular, mesenteric
- Mammary gland
- Skeletal muscle
- Skin: ventral abdomen, injection site
- Thymus, thyroid, parathyroid
Summary

- Myeloma is an incurable disease with pressing need for innovative therapeutic strategies
- MV-NIS targets myeloma cells preferentially using CD46
- Preclinical data and careful trial design lead us to believe that we can safely administer this therapeutic agent