INFECTOBESITY: OBESITY OF INFECTIOUS ORIGIN

Nikhil V Dhurandhar
Department of Nutritional Sciences
Texas Tech University
Lubbock, TX
1. The Concept
2. Animal Models
3. Mechanism of Action
4. Human Studies
5. Significance & Implications
INFECTOBESITY

1. The Concept
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Is Obesity an infectious disease?
Is Gastric ulcer an infectious disease?
Causes of gastric ulcer?

Hurry

Worry

and Curry
THE NOBEL PRIZE IN PHYSIOLOGY OR MEDICINE

Barry J. Marshall

J. Robin Warren

2005

“for their discovery of the Bacterium Helicobacter pylori and its role in Gastritis and peptic ulcer disease.”
Adipogenic pathogens

5. Avian adenovirus SMAM-1. Dhurandhar et al, 1992
Human adenovirus Ad36

1. Antigenically unique Vs 49 other human adenoviruses

2. Isolated in Germany, in 1978, from fecal sample of a girl suffering from diarrhea.

3. No overt symptoms in experimentally infected animals

4. 32 KB genome, DNA
   Early genes: E1A, E1B, E2, E3, E4,
   Late genes: L 1 to L 5.
INFECTOBESITY

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Ad36 infection increases obesity in animal models

Ad36 increases adiposity in marmosets

**Weight change**

**Body fat %**
Ad36 improves glycemic control in chow-fed mice

Ad36 increases liver glycogen and reduces lipid accumulation.

Adenovirus 36 as an Obesity Agent Maintains the Obesity State by Increasing MCP-1 and Inducing Inflammation

Ha-Na Na and Jae-Hwan Nam

C57BL6 mice

WT vs MCP1 KO mice
Reduction of adenovirus 36-induced obesity and inflammation via the use of mulberry extract.

Na HN¹, Park S, Jeon HJ, Kim HB, Nam JH.
Prevention of Ad36-induced obesity

SHORT COMMUNICATION

Proof-of-concept for a virus-induced obesity vaccine; vaccination against the obesity agent adenovirus 36

H-N Na and J-H Nam
Additional properties about Ad36-induced obesity

No overt symptoms / mortality

Horizontal transmission to cage-mates

Blood borne transmission: Koch’s postulate

Not much impact on food intake or activity
1. The Concept

2. Animal Models

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5. Significance & Implications
A Human Adenovirus Enhances Preadipocyte Differentiation

Sharada D. Vangipuram, * Jonathan Sheele, * Richard L. Atkinson, ‡ Thomas C. Holland, † and Nikhil V. Dhurandhar* †

Adipogenic Human Adenovirus Ad-36 Induces Commitment, Differentiation, and Lipid Accumulation in Human Adipose-Derived Stem Cells

Magdalena Pasarica,* Nazar Mashtalir,* Emily J. McAllister,* Gail E. Kilroy,* Juraj Koska,b Paska Permana,b Barbora de Courten,b,c Minghuan Yu,d Eric Ravussin,a Jeffery M. Gimble,a and Nikhil V. Dhurandhar* a

Adipogenic Cascade Can Be Induced Without Adipogenic Media by a Human Adenovirus

Miloni A. Rathod1,2, Pamela M. Rogers2, Sharada D. Vangipuram1, Emily J. McAllister2 and Nikhil V. Dhurandhar2

ORIGINAL ARTICLE

Novel genes and cellular pathways related to infection with adenovirus-36 as an obesity agent in human mesenchymal stem cells

H-N Na1,3, H Kim2,3 and J-H Nam1
Mechanism of action

Adipose tissue expansion by increasing proliferation, commitment, differentiation and lipid accumulation in adipocyte progenitors / ASC
Ad36 increases lipid accumulation

3T3-L1 cells 5-d post MDI treatment

A. Control, No Ad-36  B. Ad-36 inoculated
Characterization of the viral effects

Lipid accumulation in response to Ad36 dose

Anti-viral drug reduces lipid accumulation

**Active Ad-36 is required for lipid accumulation**
Lipid accumulation is specific to Ad36 infected hASC


Adipogenic Human Adenovirus Ad-36 Induces Commitment, Differentiation, and Lipid Accumulation in Human Adipose-Derived Stem Cells

Magdalena Pasarica,* Nazar Mashtalir,* Emily J. McAllister,* Gail E. Kilroy,* Juraj Koska, b Paska Permana, b Barbora de Courten, b,c Minghuan Yu, d Eric Ravussin, a Jeffery M. Gimble, a Nikhil V. Dhurandhar*
Ad36 INCREASES GLUCOSE UPTAKE

In diabetic and non-diabetic human adipose tissue:


In human skeletal muscle cells:

Adipocyte progenitors

1. Increased adiposity
2. Enhanced glucose clearance

Greater glucose uptake
Lipid accumulation
Greater de novo lipogenesis

Glucose

Rogers et al, *Diabetes*. 2008
Adenoviral genes

- **Early genes**
  - E1A, E1B, E2, E3, E4

- **Late genes**
  - L1, L2, L3, L4, L5

ORIGINAL ARTICLE

Human adenovirus Ad-36 induces adipogenesis via its E4 orf-1 gene

PM Rogers\(^1\)\(^\text{,}\) KA Fusinski\(^2\)\(^\text{,}\) MA Rathod\(^1\)\(^\text{,}\)\(^\text{,}\) SA Loiler\(^1\)\(^\text{,}\) M Pasarica\(^1\)\(^\text{,}\) MK Shaw\(^2\)\(^\text{,}\) G Kilroy\(^1\)\(^\text{,}\) GM Sutton\(^1\)\(^\text{,}\) EJ McAllister\(^1\)\(^\text{,}\) N Mashtalir\(^1\)\(^\text{,}\) JM Gimble\(^1\)\(^\text{,}\) TC Holland\(^2\) and NV Dhurandhar\(^1\)

\(^1\)Department of Infections and Obesity, Pennington Biomedical Research Center, Louisiana State University, Baton Rouge, LA, USA and \(^2\)Wayne State University, Detroit, MI, USA
INFECTOBESITY

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Do certain infections cause human obesity?

Challenges:

1. Obesity has insidious onset.
2. Multiple etiological factors – difficult to attribute to a factor.
3. A combination of infection with other factors needed?
4. Ethical reasons preclude experimental infection of humans.
Natural exposure to Ad36 in humans (n=505) (presence of neutralizing antibodies)

Int J Obes. 2005;29(3):281-6

1) Ad36 seropositive subjects:
   a) 30% prevalence in obese but 11% in non-obese
   b) Significantly greater BMI

2) Ad2 & Ad31 did not show this relationship
Ad36 exposure: Cross-sectional association

Twin Study

Body weight of twins is similar

Hypothesis:

Ad36 infected co-twins will be heavier compared to uninfected co-twins.
Twin pairs (n=26) discordant for Ad-36 antibodies

<table>
<thead>
<tr>
<th></th>
<th>Antibody +</th>
<th>Antibody -</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>33.0 ± 15.7</td>
<td>33.0 ± 15.7</td>
</tr>
<tr>
<td>Sex (% F / M)</td>
<td>77 / 23</td>
<td>77 / 23</td>
</tr>
<tr>
<td>BMI: (kg/m²)</td>
<td><strong>24.5 ± 5.2</strong></td>
<td>23.1 ± 4.5*</td>
</tr>
<tr>
<td>Body fat (%)</td>
<td>29.6 ± 9.5</td>
<td>27.5 ± 9.9**</td>
</tr>
</tbody>
</table>

Ad36 exposure: Cross-sectional association

1,500 Caucasian, Hispanic, African American men, women and children screened for the presence of Ad36 antibodies.

*Adjusted for age, sex, race & adiposity.

Ad36 infection was associated with
a. Better glycemic control
b. Lower hepatic lipid levels

1,400 men & women screened for exposure to Ad36

10 years later

Ad36 +
Greater increase in body fat

Ad36 +
Less decline in glucose control

Lin WY et al. Diabetes Care, Nov 2012
Rise in Ad36 Infection in Lean Swedes

Lavebratt et al, PLoS One, ‘12

From: Obesity – A Threat to Public Health?
Charlotte Lohdahl, 2007

<table>
<thead>
<tr>
<th>Participants</th>
<th>Country</th>
<th>Adenovirus screened</th>
<th>Screening method</th>
<th>Prevalence of infection</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dhurandhar et al, 1997</td>
<td>India</td>
<td>SMAM-1</td>
<td>Antibodies by agar precipitation</td>
<td>19%</td>
<td>SMAM-1-positive participants had significantly greater bodyweight and higher BMIs and significantly lower cholesterol and triglycerides than seronegative participants.</td>
</tr>
<tr>
<td>Atkinson et al, 2005</td>
<td>USA</td>
<td>Ad36</td>
<td>Neutralising antibodies</td>
<td>Obese 30% Non-obese 11%</td>
<td>Ad36-positive individuals had significantly higher BMIs and lower cholesterol and triglycerides than seronegative counterparts. Ad36 positivity was not related to age.</td>
</tr>
<tr>
<td>Atkinson et al, 2005</td>
<td>USA</td>
<td>Ad36</td>
<td>Neutralising antibodies</td>
<td>Obese 22% Non-obese not reported</td>
<td>Among Ad36-discordant twins, the Ad36-positive twin had significantly higher BMI and more body fat than their uninfected sibling.</td>
</tr>
<tr>
<td>Pasarica et al, 2008</td>
<td>USA</td>
<td>Ad36</td>
<td>Viral DNA by nested PCR</td>
<td>27% positive for Ad36 DNA in subcutaneous adipose tissue</td>
<td>Ad36-DNA-positive participants developed eight times more adipocytes than their seronegative counterparts.</td>
</tr>
<tr>
<td>Trovato et al, 2009</td>
<td>Italy</td>
<td>Ad36</td>
<td>Neutralising antibodies</td>
<td>Obese 65% Non-obese 33%</td>
<td>Ad36-positive participants had significantly higher BMIs and waist-to-hip ratios, and were significantly older, than seronegative individuals.</td>
</tr>
<tr>
<td>Goossens et al, 2009</td>
<td>Netherlands and Belgium</td>
<td>Ad36</td>
<td>Neutralising antibodies</td>
<td>Obese 6% Non-obese 4%</td>
<td>Ad36 positivity was not associated with BMI or sex, but increased significantly with age.</td>
</tr>
<tr>
<td>Broderick et al, 2010</td>
<td>USA</td>
<td>Ad36</td>
<td>Neutralising antibodies</td>
<td>Obese 34% Non-obese 39%</td>
<td>Ad36 positivity was not associated with BMI or lipid concentrations. African Americans were more likely to be Ad36-positive than white participants. Women were significantly more likely to be Ad36-positive than men. Older people were less likely to be Ad36-positive than younger people.</td>
</tr>
<tr>
<td>Trovato et al, 2009</td>
<td>Italy</td>
<td>Ad36</td>
<td>Neutralising antibodies</td>
<td>NAFLD 32% Non-NAFLD 47%</td>
<td>Ad36 positivity was associated with higher BMI and greater fat mass in NAFLD patients than in Ad36 negative.</td>
</tr>
<tr>
<td>Na et al, 2010</td>
<td>South Korea</td>
<td>Ad36</td>
<td>Neutralising antibodies</td>
<td>Obese 29% Non-obese 14%</td>
<td>Ad36 positivity was significantly associated with an increase in BMI and higher serum cholesterol and triglyceride concentrations than being Ad36 negative.</td>
</tr>
<tr>
<td>Atkinson et al, 2010</td>
<td>South Korea</td>
<td>Ad36</td>
<td>Neutralising antibodies</td>
<td>Obese and overweight 30% Non-obese not reported</td>
<td>Ad36 positivity was significantly associated with BMI Z score and waist circumference, but not with lipid concentrations.</td>
</tr>
<tr>
<td>Gabbert et al, 2010</td>
<td>USA</td>
<td>Ad36</td>
<td>Neutralising antibodies</td>
<td>Obese 22% Non-obese 7%</td>
<td>Ad36-positive obese patients had significantly higher BMIs, waist circumferences, and waist-to-height ratios than their Ad36-negative counterparts. Ad36-positive non-obese individuals had significantly higher BMIs and waist-to-hip ratios and were significantly older than seronegative counterparts.</td>
</tr>
<tr>
<td>Salehian et al, 2010</td>
<td>USA</td>
<td>Ad36</td>
<td>Viral DNA by nested PCR</td>
<td>Adult with abnormal adiposity was positive for Ad36 DNA in adipose tissue. Two of eight obese adults without abnormal fat were positive for Ad36 DNA.</td>
<td>Ad36 DNA is present in adipose tissue of obese participants. Abnormal adiposity was associated with Ad36 DNA in adipose tissue.</td>
</tr>
</tbody>
</table>

BMI=body-mass index NAFLD=non-alcoholic fatty liver disease.
Ad36 studies

Korea, China

Australia

USA:
CA, GA, MD, MO, (WI, MI, LA, VA)
Canada; Mexico

Sweden, Belgium, The Czech Republic; Italy; Poland, Turkey
Association of Adenovirus 36 Infection with Obesity and Metabolic Markers in Humans: A Meta-Analysis of Observational Studies

Tomohide Yamada, Kazuo Hara, Takashi Kadowaki
Department of Diabetes and Metabolic Diseases, Graduate School of Medicine, University of Tokyo, Japan

**Ad36 & BMI**
3.19 (1.44, 4.93), P<0.001;

**Ad36 & Obesity**
1.90 (1.01, 3.56), P=0.047;
Serological data analyses show that adenovirus 36 infection is associated with obesity: A meta-analysis involving 5739 subjects.


Ad36 infection in humans is associated with greater differentiation potential of preadipocytes

- Pima Indian subjects
- Sub-q fat screened
- 27% subjects had Ad-36 DNA
- DNA + subjects had greater preadipocyte differentiation
In subjects with high body fat, Ad36 correlated positively with adiposity, and negatively with bone strength.
An Observational Study of the Association between Adenovirus 36 Antibody Status and Weight Loss among Youth

Jillon S. Vander Wal\textsuperscript{a}  Jean Huelsing\textsuperscript{b}  Olga Dubuisson\textsuperscript{c}  Nikhil V. Dhurandhar\textsuperscript{c}

\textsuperscript{a}Department of Psychology, Saint Louis University, St. Louis, MO, \textsuperscript{b}Living Well Foundation, Imperial, MO, \textsuperscript{c}Pennington Biomedical Research Center, Louisiana State University System, Baton Rouge, LA, USA
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OBESITY

A complex disease with multi-factorial etiology.

A multi-factorial treatment and prevention approach.

BETTER RESULTS?
1. Unique prevention & treatment strategies for:

   Ad36-induced obesity

2. A vaccine is perhaps easier than behavioral change

3. Eliminating Ad36 from environment – not needed
Summary

• Infection with Ad36 causes obesity in animals and is correlated with human obesity

• Other adipogenic pathogens?

• Have infections contributed to the increase in prevalence of obesity since 1980?
Asthma
Influenza
Obesity
Asthma 2004
*This map indicates geographic spread and does not measure the severity of influenza activity.*
*This map indicates geographic spread and does not measure the severity of influenza activity.
*This map indicates geographic spread and does not measure the severity of influenza activity.*
A Weekly Influenza Surveillance Report Prepared by the Influenza Division
Weekly Influenza Activity Estimates Reported by State and Territorial Epidemiologists*

Week Ending November 15, 2008- Week 46

*This map indicates geographic spread and does not measure the severity of influenza activity.
FLUVIEW
A Weekly Influenza Surveillance Report Prepared by the Influenza Division
Weekly Influenza Activity Estimates Reported by State and Territorial Epidemiologists*

Week Ending November 22, 2008 - Week 47

*This map indicates geographic spread and does not measure the severity of influenza activity.
*This map indicates geographic spread and does not measure the severity of influenza activity.*
A Weekly Influenza Surveillance Report Prepared by the Influenza Division
Weekly Influenza Activity Estimates Reported by State and Territorial Epidemiologists*

Week Ending January 03, 2009 - Week 53

*This map indicates geographic spread and does not measure the severity of influenza activity.
A Weekly Influenza Surveillance Report Prepared by the Influenza Division
Weekly Influenza Activity Estimates Reported by State and Territorial Epidemiologists*

Week Ending January 17, 2009 - Week 2

*This map indicates geographic spread and does not measure the severity of influenza activity.
*This map indicates geographic spread and does not measure the severity of influenza activity.*
FLUVIEW

A Weekly Influenza Surveillance Report Prepared by the Influenza Division
Weekly Influenza Activity Estimates Reported by State and Territorial Epidemiologists*

Week Ending February 07, 2009 - Week 5

*This map indicates geographic spread and does not measure the severity of influenza activity.
A Weekly Influenza Surveillance Report Prepared by the Influenza Division
Weekly Influenza Activity Estimates Reported by State and Territorial Epidemiologists*

Week Ending February 14, 2009- Week 6

*This map indicates geographic spread and does not measure the severity of influenza activity.
A Weekly Influenza Surveillance Report Prepared by the Influenza Division
Weekly Influenza Activity Estimates Reported by State and Territorial Epidemiologists*

Week Ending February 21, 2009 - Week 7

*This map indicates geographic spread and does not measure the severity of influenza activity.
*This map indicates geographic spread and does not measure the severity of influenza activity.*
A Weekly Influenza Surveillance Report Prepared by the Influenza Division
Weekly Influenza Activity Estimates Reported by State and Territorial Epidemiologists*

Week Ending March 07, 2009 - Week 9

*This map indicates geographic spread and does not measure the severity of influenza activity.
Obesity
Obesity Trends* Among U.S. Adults
BRFSS, 1985

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1986

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1987
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults

BRFSS, 1988

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1989
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1990

(*BMI ≥30, or ~30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1991

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1992

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1993
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1994
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

No Data           <10%          10%–14%  15%–19%

[Map of obesity trends across the U.S.]
Obesity Trends* Among U.S. Adults
BRFSS, 1995

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1996
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1997

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 1998
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)

[Map showing obesity trends across the United States]
Obesity Trends* Among U.S. Adults

BRFSS, 1999

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 2000
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 2001

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults

BRFSS, 2002

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 2003

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 2004

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 2005
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 2006
(*BMI ≥30, or ~30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 2007
(*BMI ≥30, or ~30 lbs. overweight for 5’4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 2008

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 2009
(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Obesity Trends* Among U.S. Adults
BRFSS, 2010

(*BMI ≥30, or ~ 30 lbs. overweight for 5’ 4” person)
Why does the spread of obesity in the US resemble an infectious disease?
Thank you!

Batu Caves, Malaysia. March 2014
Virus-induced obesity

Implications

Exploit the anti-diabetic property
Etiology and Pathophysiology/Obesity Treatment

Harnessing the beneficial properties of adipogenic microbes for improving human health

N. V. Dhurandhar¹, L. Geurts², R. L. Atkinson³, L. Casteilla⁴, K. Clement⁵, P. Gerard⁶, M. Vijay-Kumar⁷, J. H. Nam⁸, M. Nieuwdorp⁹, G. Trovato¹⁰, T. I. A. Sørensen¹¹, A. Vidal-Puig¹² and P. D. Cani¹²
Could Ad36 proteins provide a template for designing a therapeutic target to improve hyperglycemia in humans?

**E4orf1**: a candidate protein, if it improves glycemic control in vivo.
Approaches to test *E4orf1* in vivo

1. Retrovirus expressing *E4orf1*

2. AAV expressing *E4orf1*

3. Transgenic mice with inducible, adipose tissue specific expression of *E4orf1*

4. E4orf1 chemical analogs
E4orf1: improves glycemic control in vivo !!
E4orf1 again improves GTT, 1 wk post booster injection

**Graph 1:**
- Y-axis: Glucose [mg/dL]
- X-axis: Time (0-200)
- Control, E4orf1(IP), E4orf1(MLT)
- Statistically significant differences indicated by * and **

**Graph 2:**
- Y-axis: A.U.C.
- X-axis: Control, E4orf1(IP), E4orf1(MLT)
- Statistically significant differences indicated by **
E4orf1 did not modulate ITT at 1 wk post injection
Transgenic mice with AT-specific inducible E4orf1 expression

1. Crossed TRE-Ad36-E4orf1 mice with adiponectin-rtTA mice.
2. Dox in water to expresses E4orf1 specifically within adipose tissue
C57/BL6 male  WT vs TRE-Ad36-E4orf1-adiponectin-rtTA mice following 5-wk  Dox-HFD feeding (600 mg/kg) (n = 7/group)

Glucose: OGTT

WT

Ad36-rtTA

Glucose (mg/dl)

Time (min)
C57/BL6 male WT vs TRE-Ad36-adiponectin-rtTA mice following 5-wk Dox-HFD feeding (600 mg/kg) (n = 7/group)
• **E4orf1 protein**
  
  • Independent of proximal insulin signaling  
  • Reduce insulin levels in vivo  
  • Not secretagogues, or insulin mimetic  

• **Insulin sparing action**

• **Potential applications**
  
  Type 2 diabetes  
  Type 1 diabetes  
  NAFLD
Natural Ad36 infection is associated with better glycemic control in humans.

Experimental Ad36 infection improves glycemic control and steatosis in animals.

Ad36 improves glucose disposal via its **E4orf1** gene.

We are Here

- **E4orf1**: enhances glucose disposal in vitro
- **E4orf1**: enhances glucose disposal in vivo

Develop a functional analog

Functionality in rodents

Toxicology in primates

Human trials

Our Roadmap to Develop a Novel Anti-diabetic Drug

Ad36 improves glucose disposal via its **E4orf1** gene.

Experimental Ad36 infection improves glycemic control and steatosis in animals.

Natural Ad36 infection is associated with better glycemic control in humans.
A. **United States Patents approved:**
   1. Number 6,127,113. Viral Obesity methods and Compositions.
   2. Number 6,664,050. Viral Obesity methods and Compositions.

B. **Patents filed:**
   2. Enhanced glycemic control using Ad36E4orf1 and AKT1 inhibitor.

C. **Provisional patent filed:**
Ad36 up-regulates inflammatory cytokine IL-6 in vitro

ORIGINAL ARTICLE

Infection-induced inflammatory response of adipocytes in vitro

JJM Bouwman¹, FLJ Visseren², KP Bouter³ and RJA Diepersloot¹

¹Department of Medical Microbiology and Immunology, Diakonessen Hospital Utrecht, Bosboomstraat, Utrecht, The Netherlands; ²Department of Vascular Medicine, University Medical Centre Utrecht, Heidelberglaan, The Netherlands and ³Department of Internal Medicine, Bosch Medicentre, Nieuwstraat, ‘s-Hertogenbosch, The Netherlands
Ad36 increases inflammatory cytokines mRNA in adipose tissue of mice

E4orf1 Improves Lipid and Glucose Metabolism in Hepatocytes: A Template to Improve Steatosis & Hyperglycemia

Emily J. Dhurandhar¹, Rashmi Krishnapuram¹, Vijay Hegde¹, Olga Dubuisson¹, Rongya Tao², X. Charlie Dong², Jianping Ye¹, Nikhil V. Dhurandhar¹*

¹ Pennington Biomedical Research Center, Louisiana State University System, Baton Rouge, Louisiana, United States of America, ² Department of Biochemistry and Molecular Biology, Indiana University School of Medicine, Indianapolis, Indiana, United States of America

In HepG2 cells: E4orf1
1. Reduces glucose output in basal and gluconeogenic conditions
2. Reduced de novo lipogenesis by 35%
3. Increased complete fatty acid oxidation 2-fold
4. Increases apoB secretion (fatty acid export) by 1.5 fold

1. Decreased lipid synthesis
2. Increased fatty acid oxidation
3. Increased lipid export → ? Reduced liver lipids ?