Open-label, dose-escalation study evaluating the safety of a single administration of an adenoviral vector encoding human aquaporin-1 to one parotid salivary gland in individuals with irradiation-induced parotid salivary hypofunction

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Salivary glands are made of two types of epithelia: the acinar region is a secretory epithelium and the ductal region is an absorptive epithelium.
Effect of irradiation on salivary gland structure
Salivary hypofunction leads to considerable morbidity

- Dysphagia
- Xerostomia
- Oral infections (candidiasis, caries)
- Reduced mucosal healing
- Oral pain and discomfort
Gene transfer to salivary glands is easy

General method - intraductal cannulation and retrograde infusion
Salivary glands

a “monolayer” of cells lining the ducts

Vectors introduced via the ducts have access to almost all gland cells

Cook et al, 1994
Original strategy to repair irradiation damage
Hypothesized mechanism to repair irradiation damaged gland
Schematic diagram of AdhAQP1

ΔE1 E2 E3 E4

ITR

P_{CMV} hAQP1 SV40polyA

ITR
In Vitro Experiments (MDCK cells)

Control

AdhAQP1

xy plane
xz plane

Delporte et al, PNAS, 1997
In Vitro Experiments (SMIE cells)

He et al, Pflügers Arch, 1998
Testing the strategy in vivo - rats

Timeline of initial rat IR study

- Adult rats irradiated at 17.5 Gy, 21 Gy, or sham-treated
- Addl 312 or AdhAQP1 5 x 10⁹ pfu
- Adv to 17.5 Gy rats
- Adv to 21 Gy rats
- Collect SMG saliva 3 days post-Adv administration

Delporte et al, PNAS, 1997
5x10^9 pfu/gland; MOI = 2.5x10^7 pfu/μl infusate
Testing the strategy in vivo - minipigs

Timeline of minipig IR study

Shan et al, Mol Ther, 2005
AdhAQP1 delivery improves irradiated parotid gland function in minipigs

Shan et al, Mol Ther, 2005

Parotid Flow (% Pre-IR)

Days post-irradiation

10^9 pfu/gland = 2.5x10^5 pfu/μl infusate and is ~100x < MOI used in rats
Is AdhAQP1 vector delivery to salivary glands safe? Non-GLP minipig studies*

- 100% animal survival
- No parotid swelling
- Normal saliva appearance and consistency (no purulence)
- Normal food consumption

* Similar results in non-human primate studies
Clinical lab parameters examined in minipigs pre/post Ad5 vector *

- Calcium
- Sodium
- Chloride
- Potassium
- Glucose
- BUN
- Creatinine
- Platelets
- Hemoglobin
- Total protein
- ALT
- AST
- Albumin
- Alkaline phosphatase
- Amylase
- LDH
- Globulins
- Red cells
- White cells

* Similar results in non-human primate studies  
Shan et al, Mol Ther, 2005
Is AdhAQP1 vector delivery to salivary glands safe? GLP rat studies

Table 2: Summarized results of completed GLP toxicological studies of rAd5 vector delivery to rat submandibular glands

<table>
<thead>
<tr>
<th>Vector</th>
<th>AdCMVH3</th>
<th>AdCMVhGH</th>
<th>AdhAQP1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference</td>
<td>[33]</td>
<td>[34]</td>
<td>[unaudited now]</td>
</tr>
<tr>
<td>Doses</td>
<td>≤10⁹ pfu</td>
<td>≤10¹¹ particles</td>
<td>≤2x10¹¹ particles</td>
</tr>
<tr>
<td>Length of study</td>
<td>15 days</td>
<td>28 days</td>
<td>92 days</td>
</tr>
<tr>
<td>Survival</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Clinical signs</td>
<td>no significant</td>
<td>no significant</td>
<td>no significant</td>
</tr>
<tr>
<td>Food consumption</td>
<td>no change</td>
<td>no change</td>
<td>no change</td>
</tr>
<tr>
<td>Weight gain</td>
<td>no change</td>
<td>no change</td>
<td>no change</td>
</tr>
<tr>
<td>Histopathology</td>
<td>targeted SMG</td>
<td>targeted SMG</td>
<td>not done yet</td>
</tr>
<tr>
<td>Clinical chemistry</td>
<td>no change</td>
<td>globulin increased</td>
<td>no change</td>
</tr>
<tr>
<td>Hematology</td>
<td>NR¹</td>
<td>no change</td>
<td>see below</td>
</tr>
<tr>
<td>RCA</td>
<td>none detected</td>
<td>none detected</td>
<td>not done yet</td>
</tr>
</tbody>
</table>

N = 120 AdCMVH3; 144 AdCMVhGH; 200 AdhAQP1; equal #s m, f

Note: Maximum AdhAQP1 dose is twice the maximum total dose, and 10-fold the maximum MOI (in particles/μl), for the proposed clinical study
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Dosing assumes a 15:1 pu:pfu ratio and 1000μl infusion volume. Note that in minipigs the effective total dose = 10^9 pfu/gland, i.e., a MOI = 2.5 x 10^5 pfu/μl infusate (4000μl total)