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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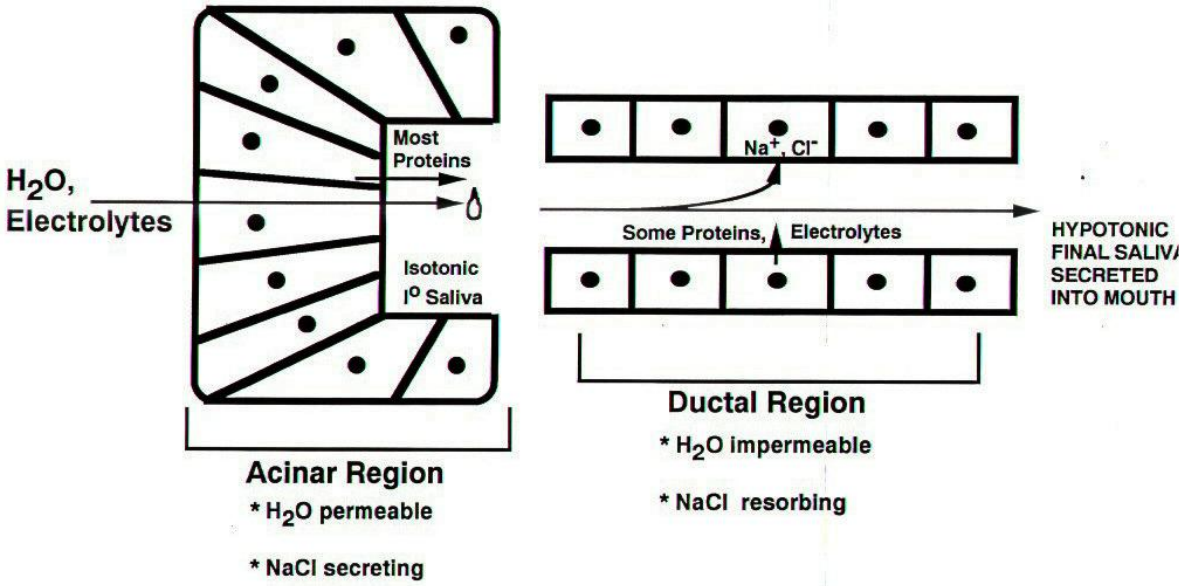
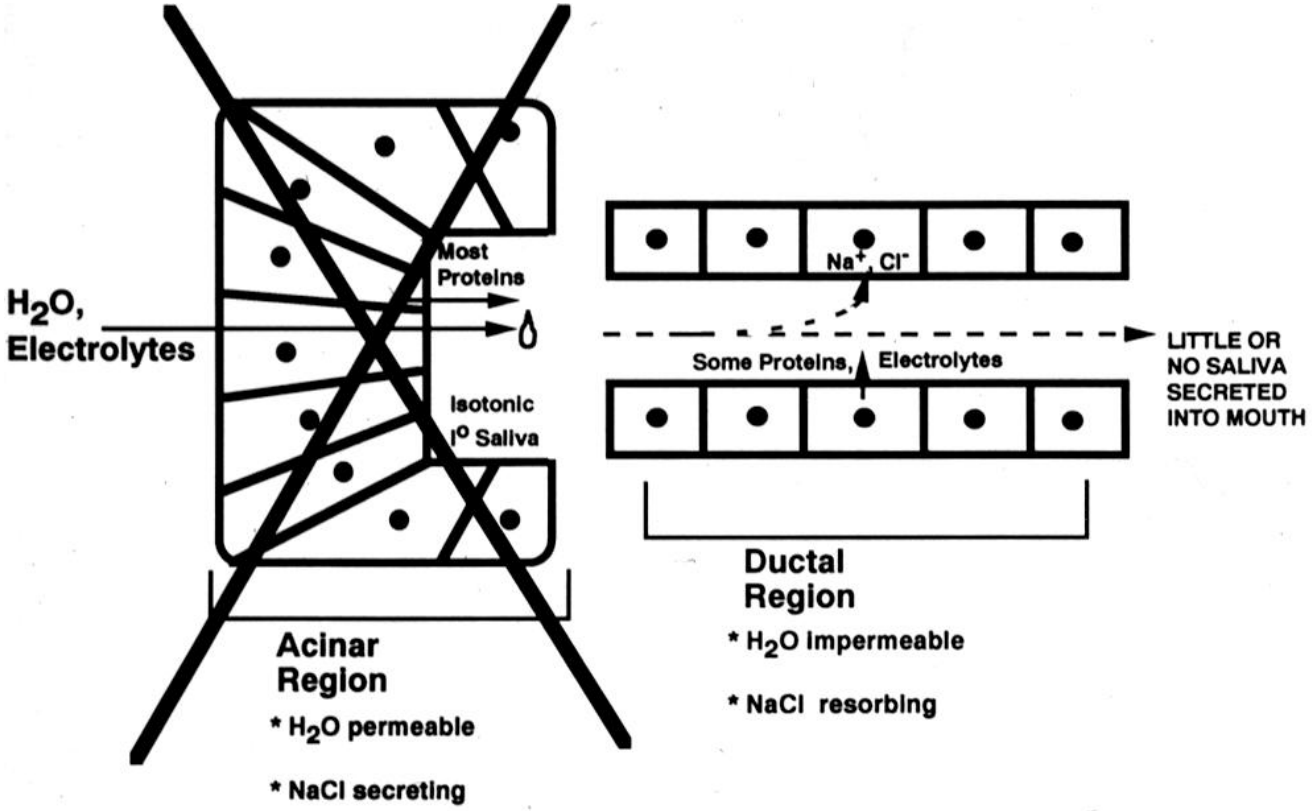
Review of salivary gland biology



Salivary glands are made of two types of epithelia:
the acinar region is a secretory epithelium
the ductal region is an absorptive epithelium

Effect of irradiation on salivary gland structure



Salivary hypofunction leads to considerable morbidity

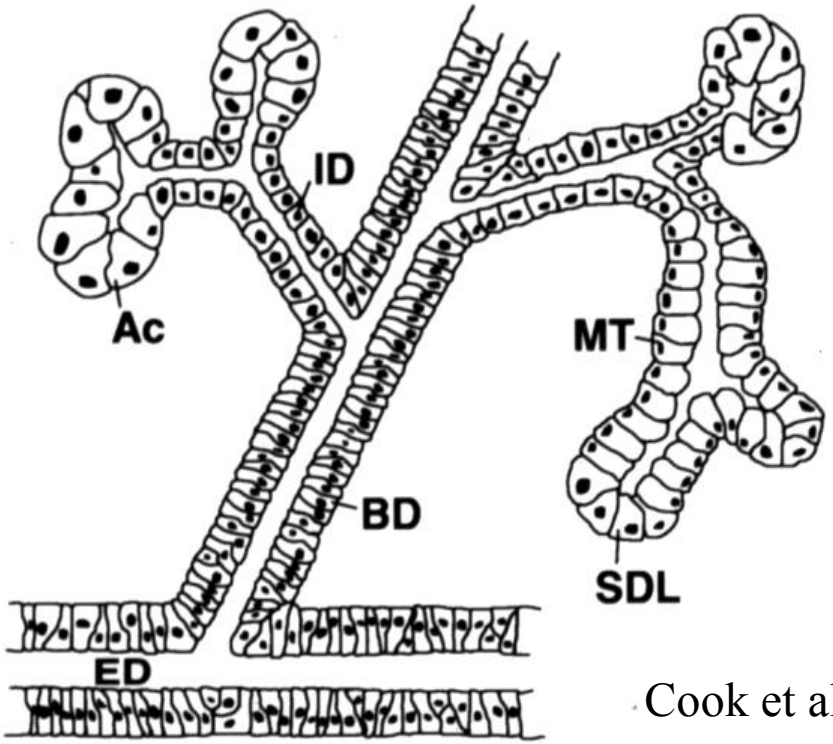
- Dysphagia
- Xerostomia
- Oral infections (candidiasis, caries)
- Reduced mucosal healing
- Oral pain and discomfort

Gene transfer to salivary glands is easy

General method - intraductal cannulation and retrograde infusion

Salivary glands

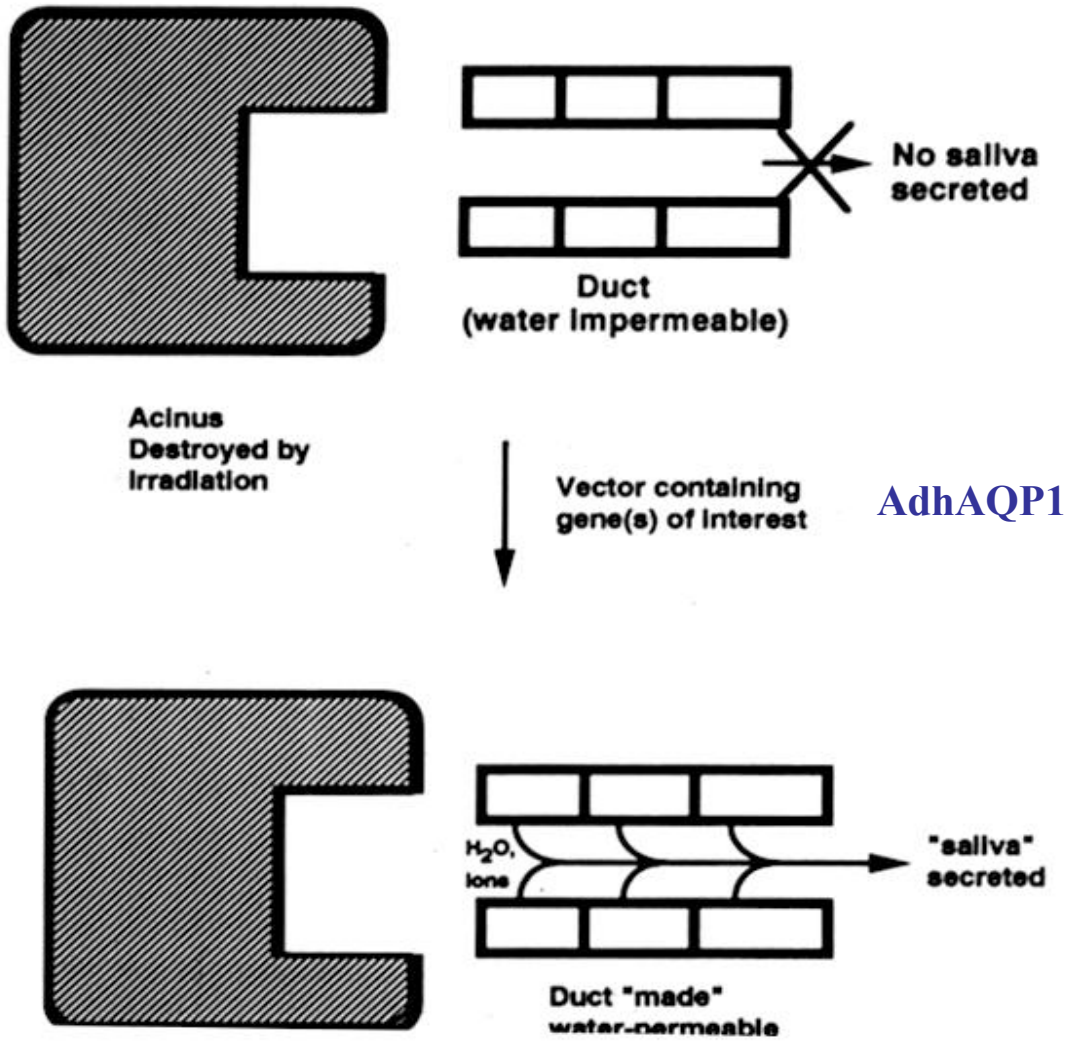
a “monolayer” of cells lining the ducts



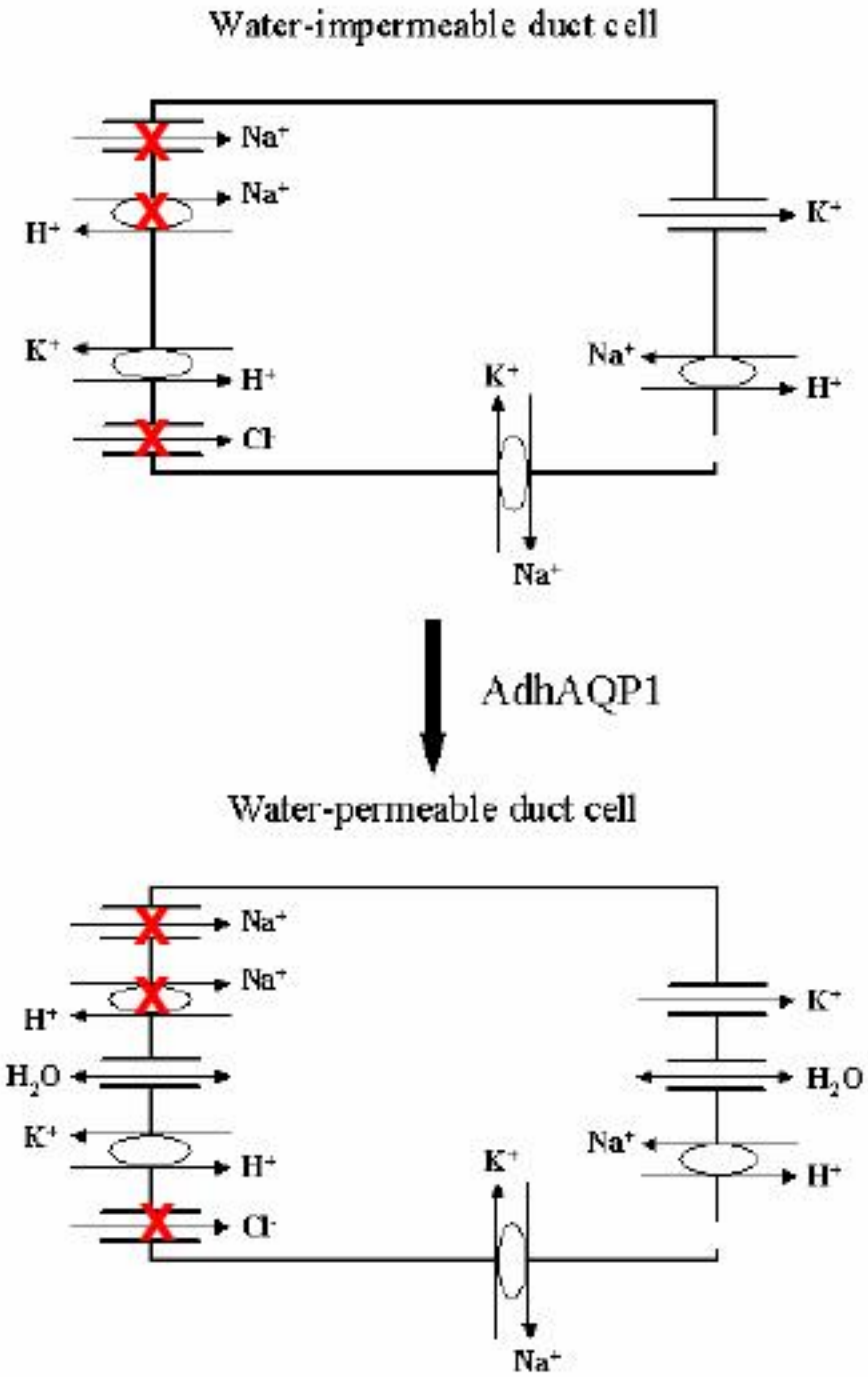
Cook et al, 1994

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

Delporte et al, PNAS, 1997

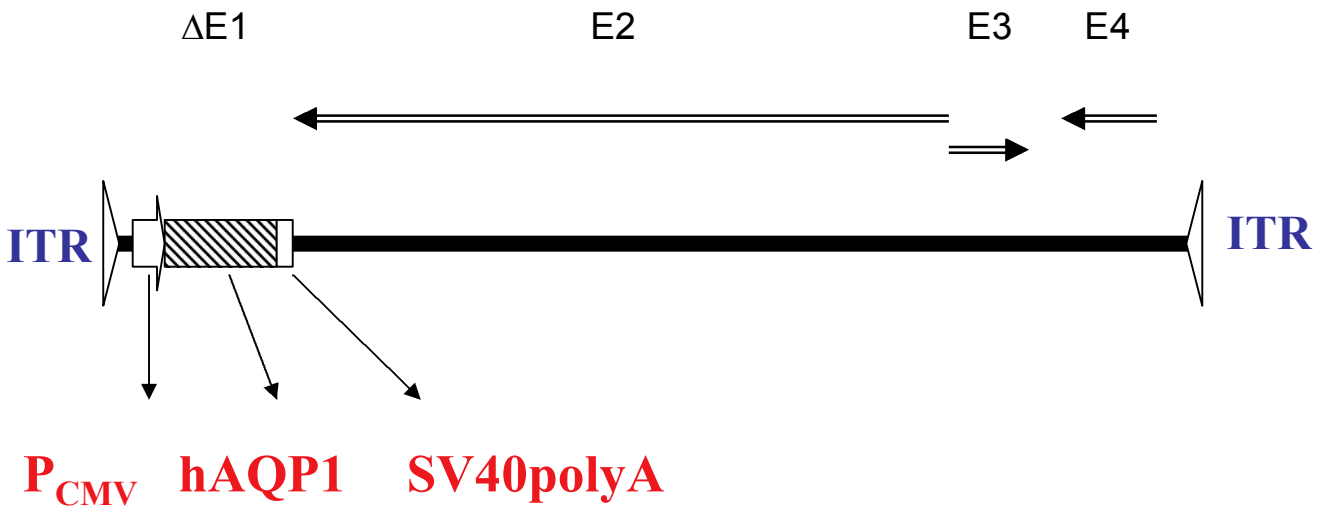


Original strategy to repair irradiation damage



Hypothesized mechanism to repair irradiation damaged gland

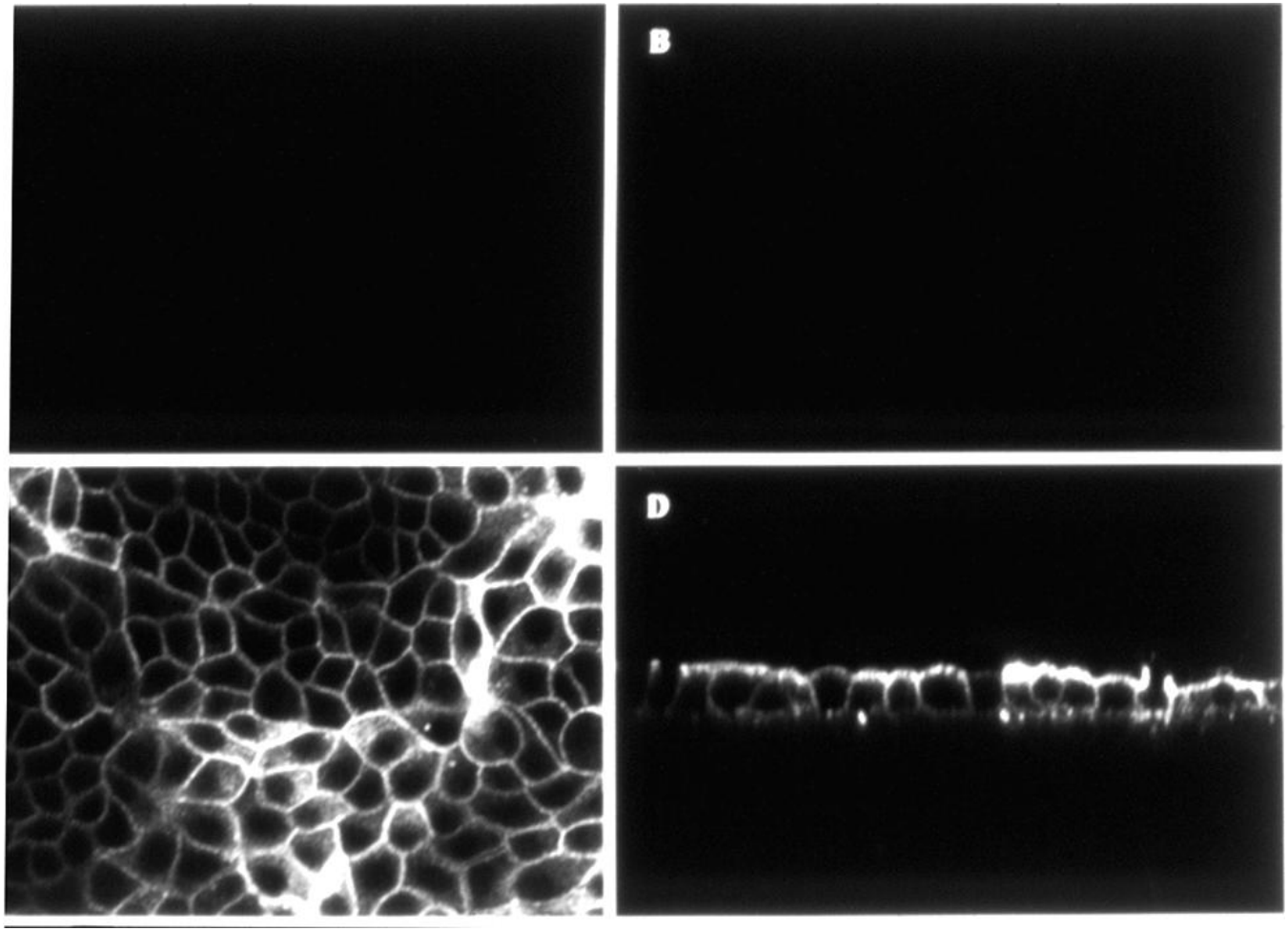
Schematic diagram of AdhAQP1



In Vitro Experiments (MDCK cells)

Control

AdhAQP1

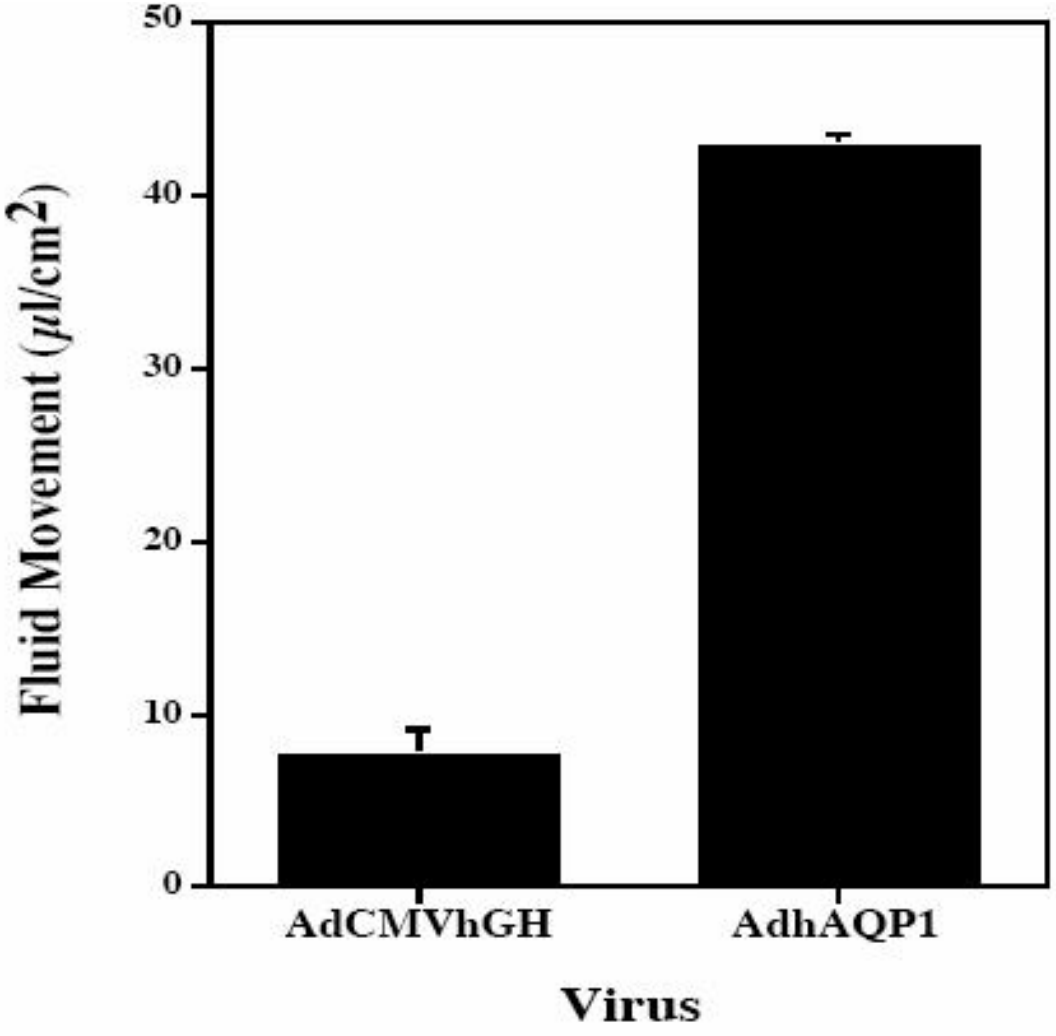


xy plane

xz plane

Delporte et al, PNAS, 1997

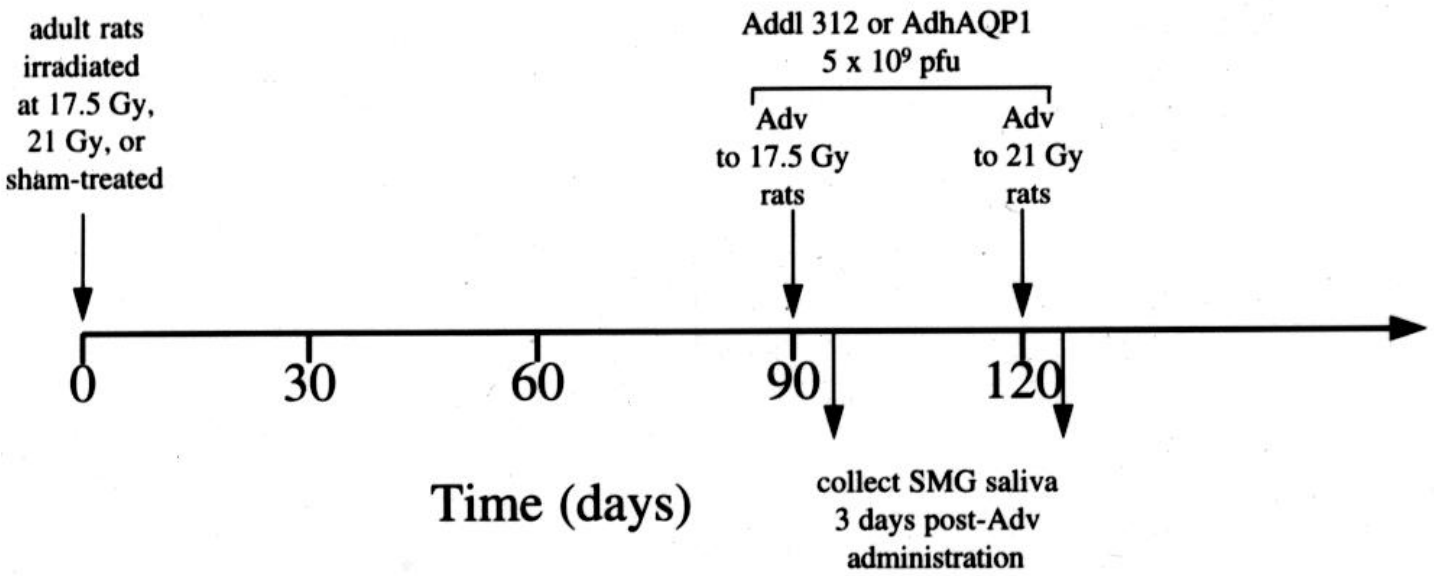
In Vitro Experiments (SMIE cells)



He et al, Pflügers Arch, 1998

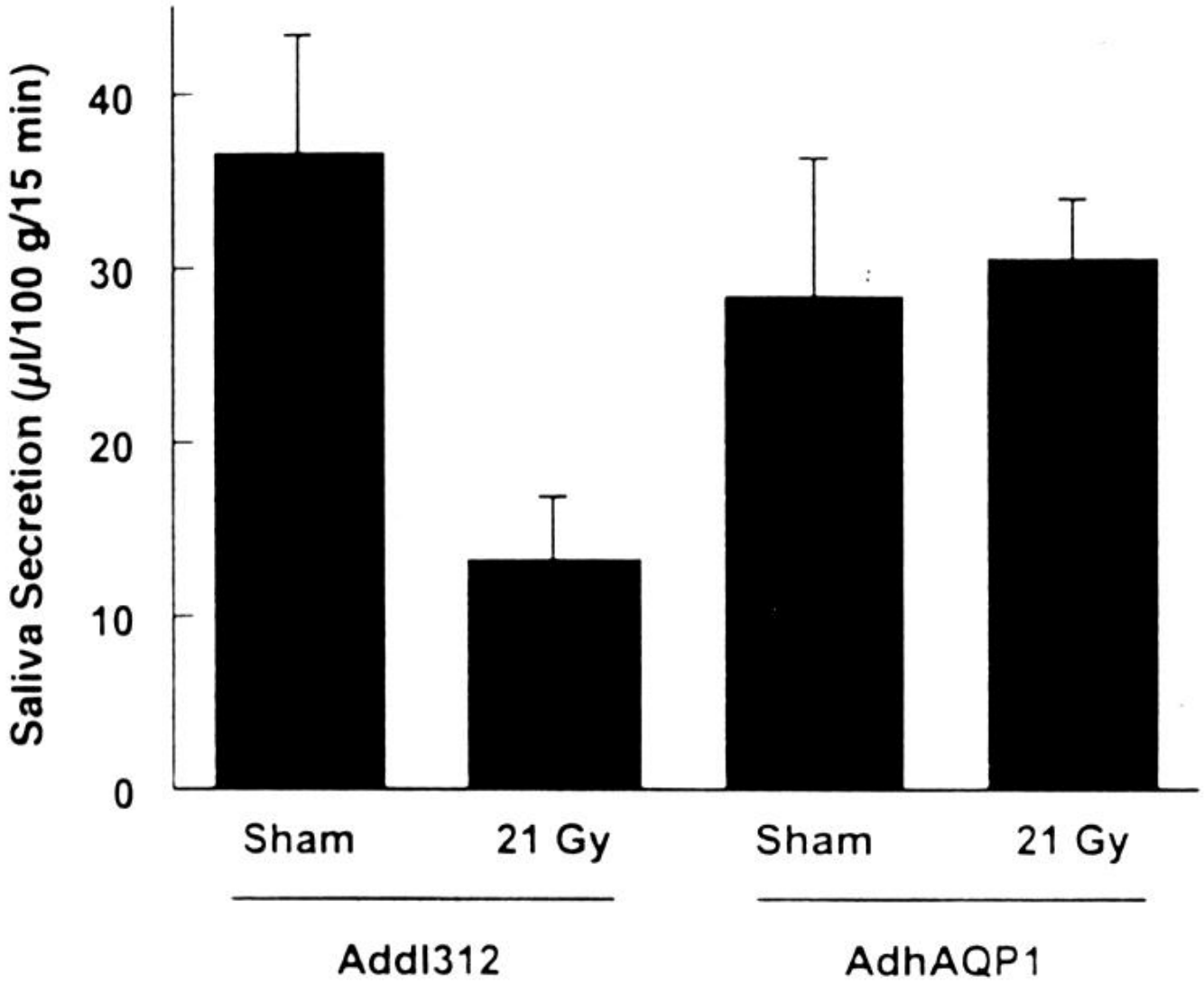
Testing the strategy in vivo - rats

Timeline of initial rat IR study



Delporte et al, PNAS, 1997

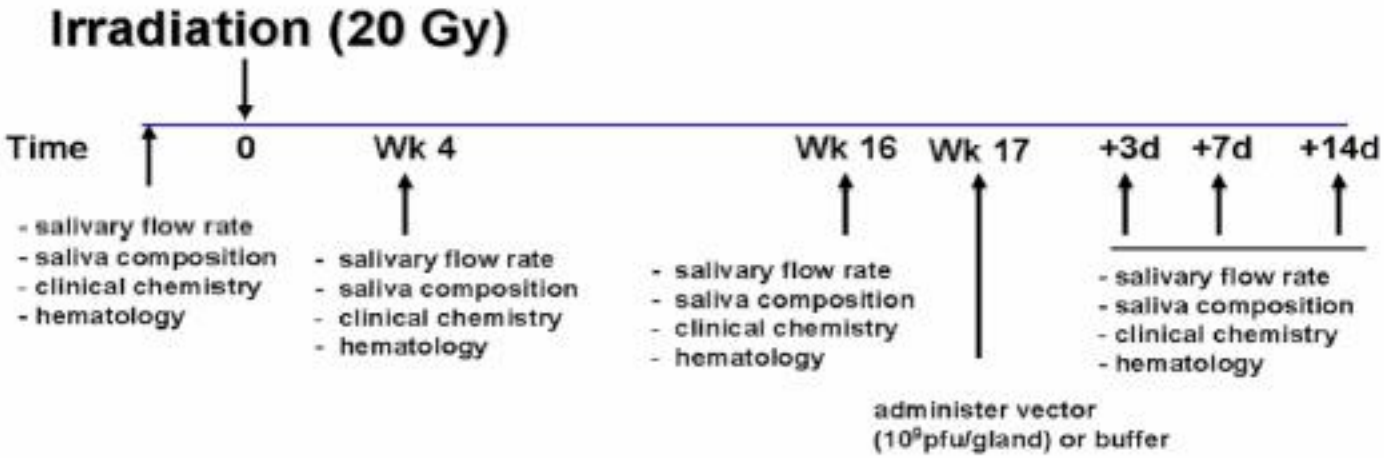
Delporte et al, PNAS, 1997



$5x10^9$ pfu/gland; MOI = $2.5x10^7$ pfu/µl infusate

Testing the strategy in vivo - minipigs

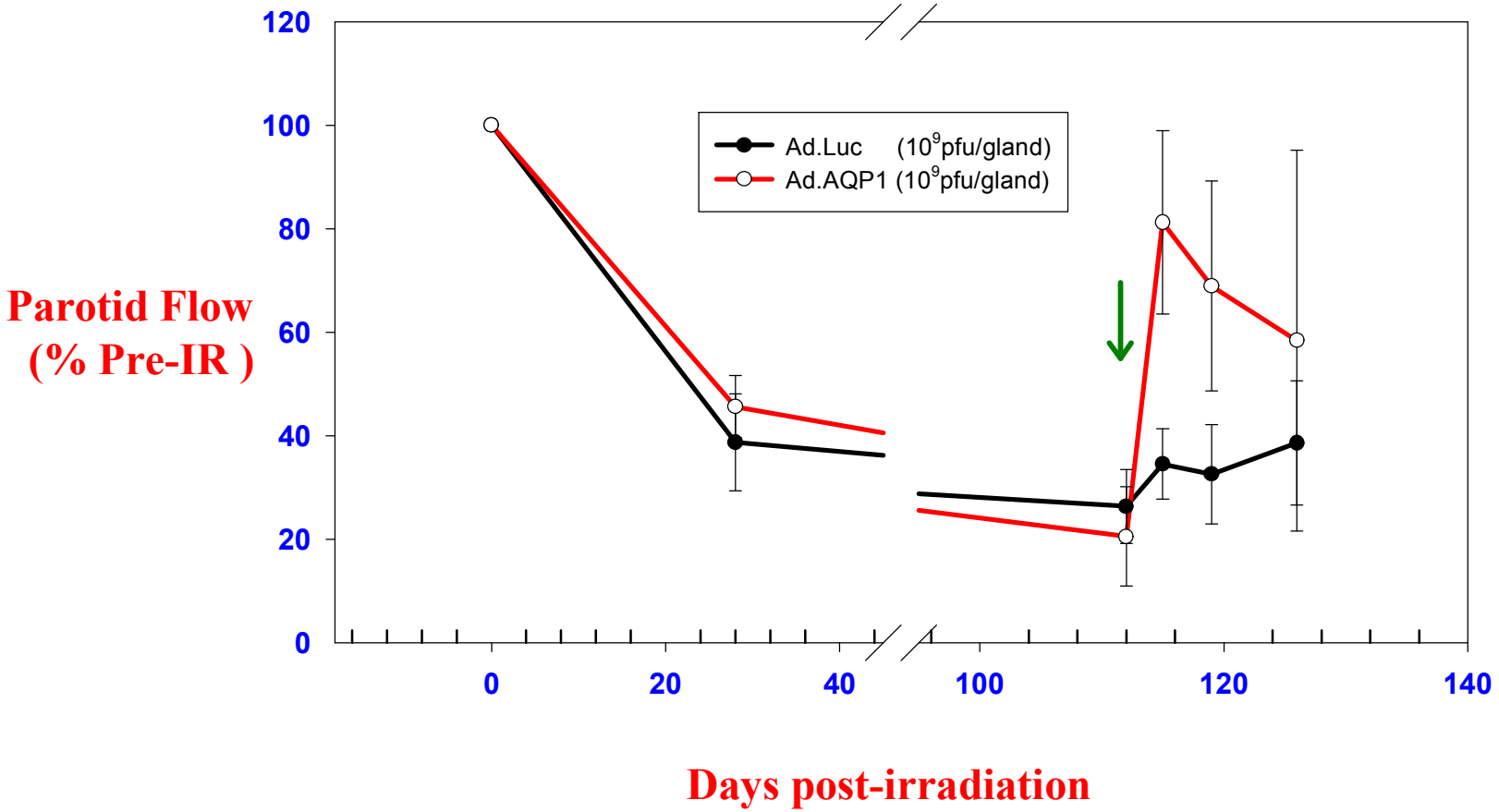
Timeline of minipig IR study



Shan et al, Mol Ther, 2005

AdhAQP1 delivery improves irradiated parotid gland function in minipigs

Shan et al, Mol Ther, 2005



10^9 pfu/gland = $2.5x10^5$ pfu/µl infusate and is ~100x < MOI used in rats

Shan et al, Mol Ther, 2005

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 [a]

Vector	AdCMVH3	AdCMVhGH	AdhAQP1
Reference	[33]	[34]	[unaudited now]
Doses [b]	$\leq 10^9$ pfu	$\leq 10^{11}$ particles	$\leq 2 \times 10^{11}$ particles
Length of study	15 days	28 days	92 days
Survival [c]	100%	100%	100% [j]
Clinical signs [d]	no significant	no significant	no significant
Food consumption	no change	no change	no change [k]
Weight gain	no change	no change	no change [l]
Histopathology [e]	targeted SMG	targeted SMG	not done yet
Clinical chemistry [f]	no change	globulin increased	no change [m]
Hematology [g]	NR [i]	no change	see below [n]
RCA [h]	none detected	none detected	not done yet

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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Patient number	Dose in particle units	"MOI" in pfu/ uL infusate
1-3	1.4×10^{8}	9.3×10^{3}
4-6	8.4×10^{8}	5.6×10^{4}
7-9	3.75×10^{9}	2.5×10^{5}
10-12	1.67×10^{10}	1.1×10^{6}
13-15	1×10^{11}	6.7×10^{6}

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 = 2.5×10^5 pfu/µl infusate (4000µl total)