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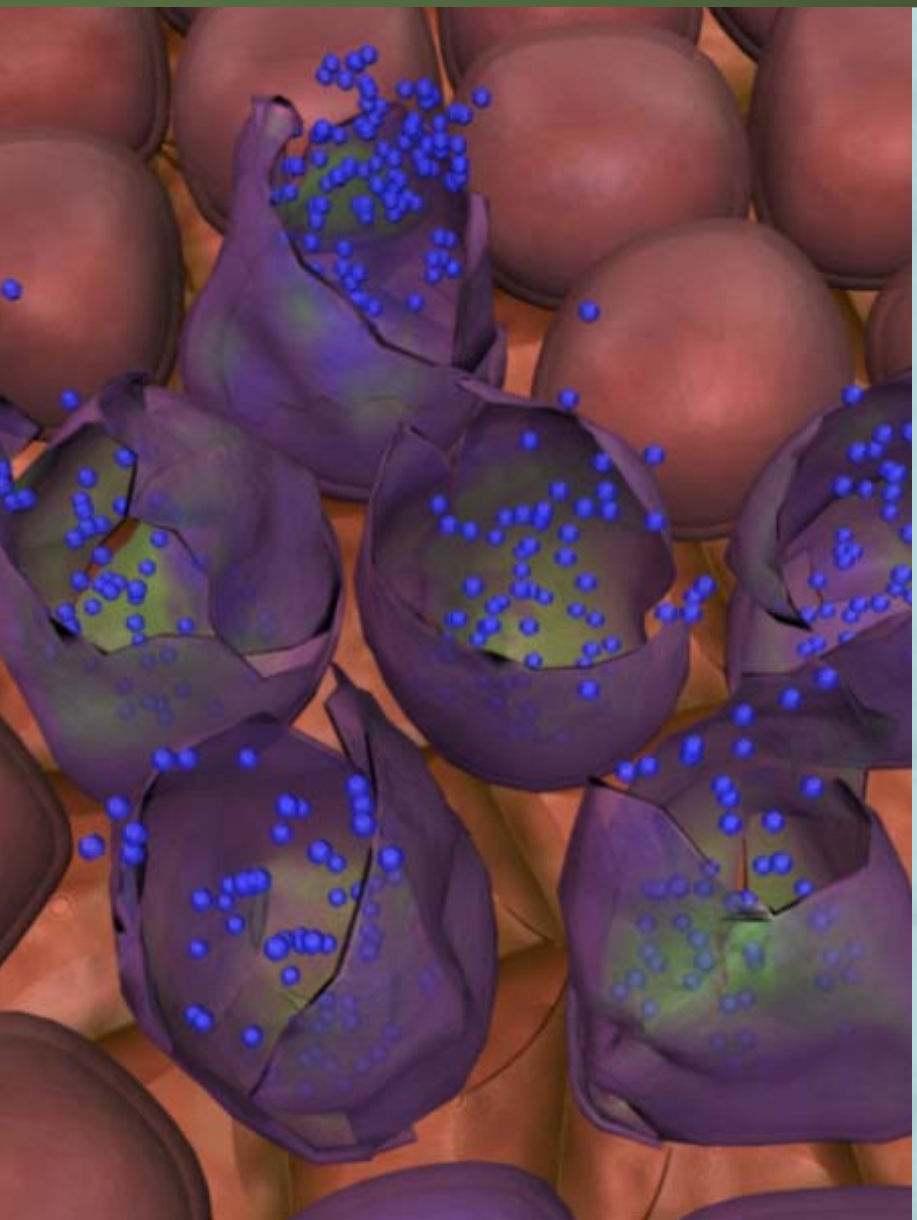
Technology Changing Life

International Society for Biological Therapy of Cancer
2008 Oncology Biologics Development Primer

Oncolytic Viruses: Reovirus

REOLYSIN® - mode of action



- REOLYSIN contains the reovirus, a naturally occurring, replication competent oncolytic virus
  - Not a gene therapy agent so no interaction with GTA (UK)
  - Not recombinant so no interaction with NIH DNA RAC (US)
- Asymptomatic in humans (does not cause disease)
- Replicates in Ras-activated cancer cells resulting in cell death

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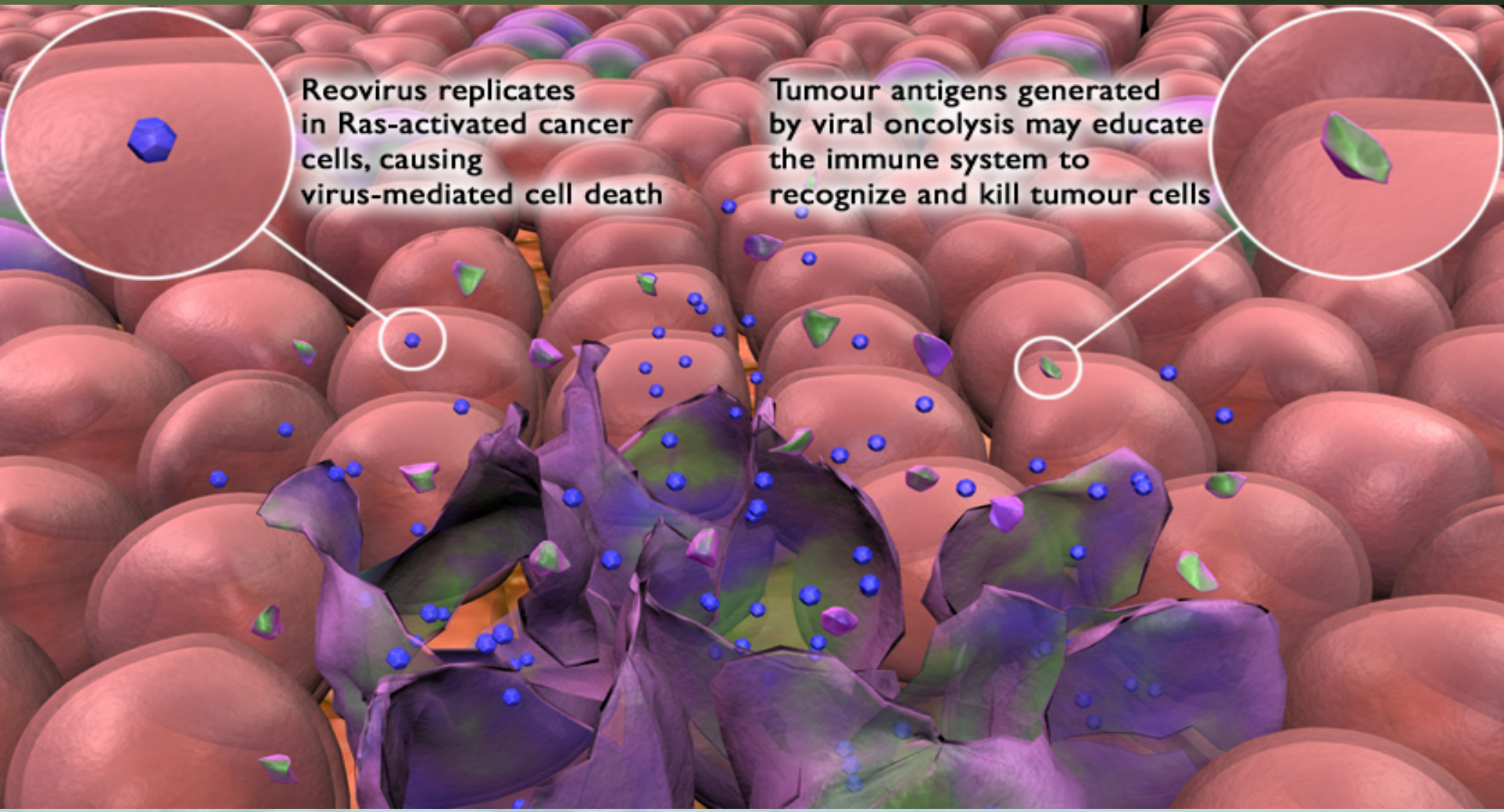
Two methods of tumor killing



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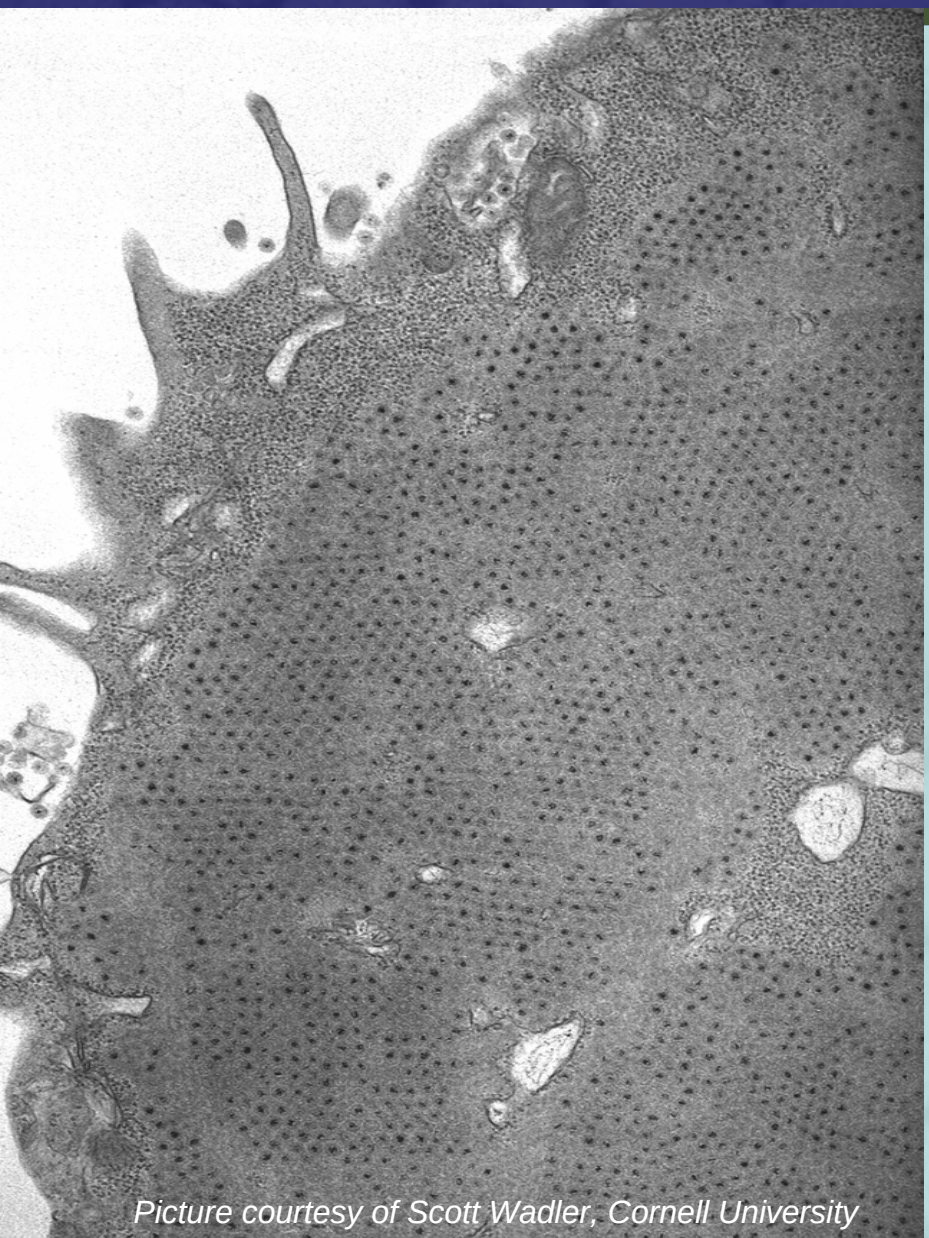
Replication



Picture courtesy of Scott Wadler, Cornell University

- Fully replication-competent
- Replication is exclusively cytoplasmic
- Proof of viral replication in tumors following systemic delivery
- Mammalian permissive therefore effective modeling in murine and non-human primate models

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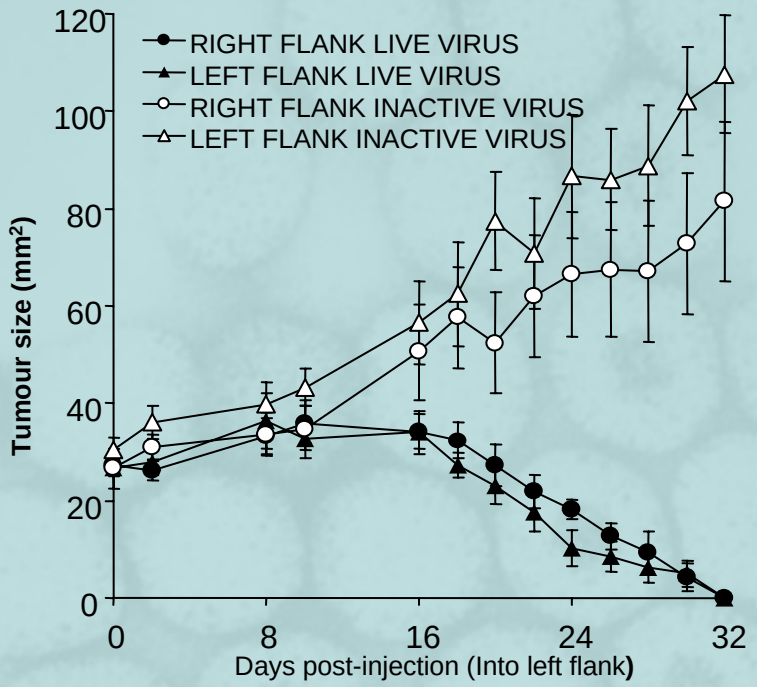
Preclinical toxicology – unique challenges

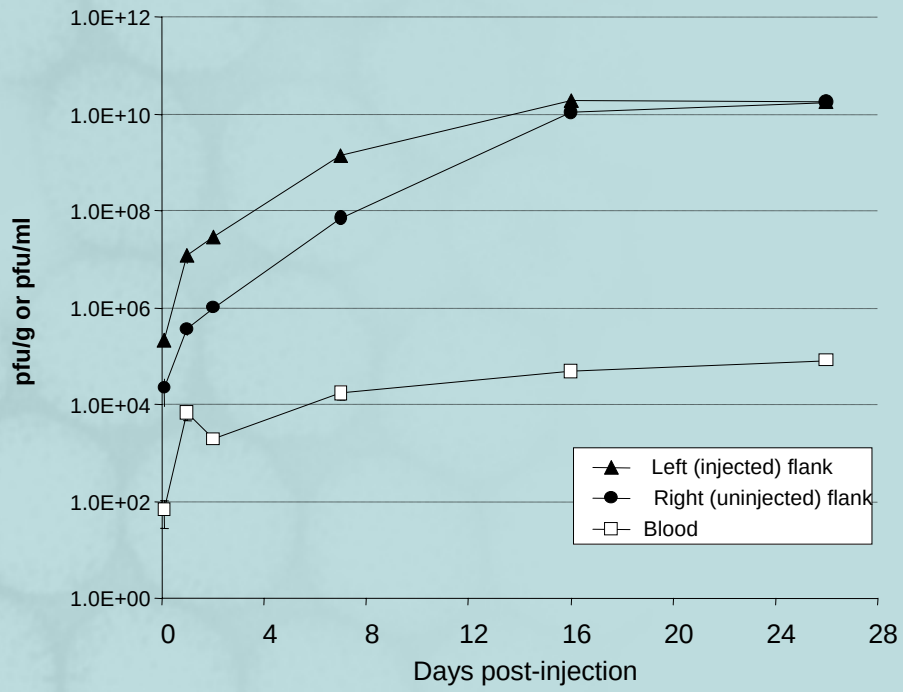
- Reovirus replicates in target cells
- Non-tumor bearing animals will not have the ability to replicate the virus
  - Input virus could be significantly less than virus amplified in tumor tissue
  - Animals bearing tumors with actively replicating virus experience prolonged virus exposure
  - Various chemotherapeutic agents can increase progeny virus production
  - Lytic release of tumor associated antigens cannot be modeled in non-tumor bearing animals

Tumor regression and viral amplification

A. REOLYSIN Induced Local and Remote Tumor Regression in Breast Cancer Xenografts



B. Viral Amplification in Xenograft



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Clinical Development Strategy

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Appropriate Toxicology Modeling

Clinical development strategy

From local to systemic, monotherapy to combination

- Local or regional administration using REOLYSIN as a monotherapy
- Systemic administration using REOLYSIN as a monotherapy
- Combination therapy using REOLYSIN locally, regionally or systemically with radiation or chemotherapy

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Preclinical toxicology - changing route of administration increases commitment to toxicology

Thirteen GLP safety studies – consistent results

Three routes of administration

- SubQ, intracerebral, and intravenous

Three animal species

- Rat, canine, primate

Single and multiple dose studies

- 28-day infusion studies completed in 3 species

No product-related severe adverse events or dose-limiting toxicities in immune competent animals

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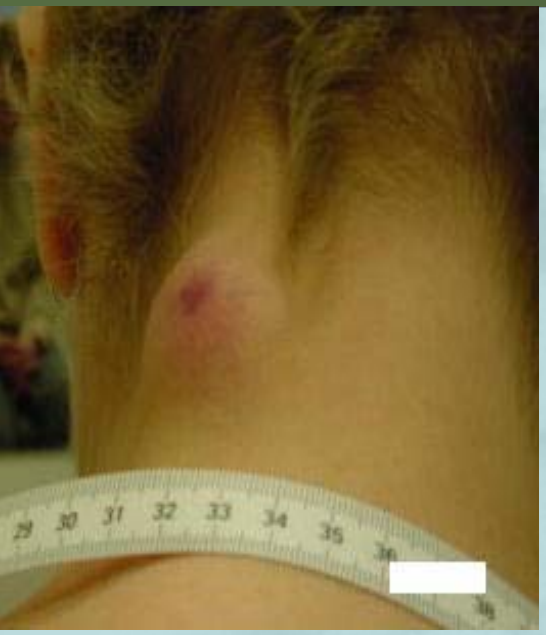
Why start with local administration?

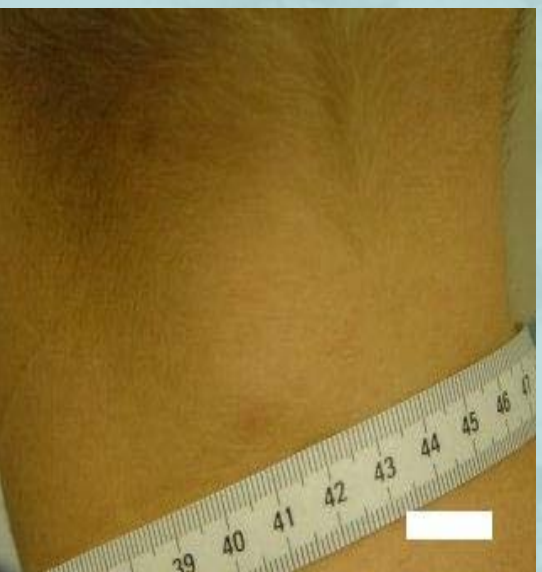
Although local administration is not as clinically relevant as systemic treatment, there are advantages:

- Considered “safer” than repeat systemic administration
- Proof of concept – could assure virus delivery to tumor
  - Activity could be measured by local response, systemic response, and superficial lesions can easily be biopsied pre and post treatment
- Requires less virus than systemic administration

If the above criteria were met (i.e. safe, demonstration of tumor regression, and improved manufacturing) then move to systemic administration

Results – Phase I intratumoral





- Dose escalation from $1x10^7$ to $1x\ 10^{10}$ $TCID_{50}$ given a single or multiple injections
  - •No anaphylaxis seen in multiple injection cohorts
- No severe adverse events noted, no DLTs, MTD not reached
- Viral activity detected in 11 of 18 patients (>30% 2-D tumor regression)
- Evidence of field effects noted in several patients
- Results mostly mirror preclinical results
- During this period improvements to manufacturing were implemented, with resulting increases in yield from 4% to 40%

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Preclinical Toxicology

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Intravenous Delivery

Repeat IV studies

Species	Dose in $TCID_{50}$	Frequency	Result
Spraque-Dawley Rats	2.1×10^6 2.1×10^7 2.1×10^8	Once daily for 28 days	No compound-related effects produced on any of the parameters assessed in this study.
Beagle Dog	7.1×10^7 7.1×10^8 7.1×10^9	Once daily for 28 days	No compound-related effects produced on any of the parameters assessed in this study
Primate	5.0×10^7 5.0×10^8 5.0×10^9	Once daily for 28 days	Dosing and recovery phases completed. No observed morbidity or mortality. EKGs conducted on day one and during week two demonstrated no abnormalities.

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Systemic administration studies

Phase I systemic administration study at the Royal Marsden Hospital and St. George's Hospital, UK

- Intravenous administration in patients with advanced or metastatic solid tumors refractory to standard therapy
- Examined dose frequency, dose escalation, retreatment (4 week cycle), and a treatment arm at the MTD
- Enrolment from May '04 – Nov '06

Phase I systemic administration study at the Montefiore Medical Center, US

- Intravenous administration in patients with advanced or metastatic solid tumors refractory to standard therapy
- Examined dose escalation
- Enrolment from Nov '05 – Oct '06

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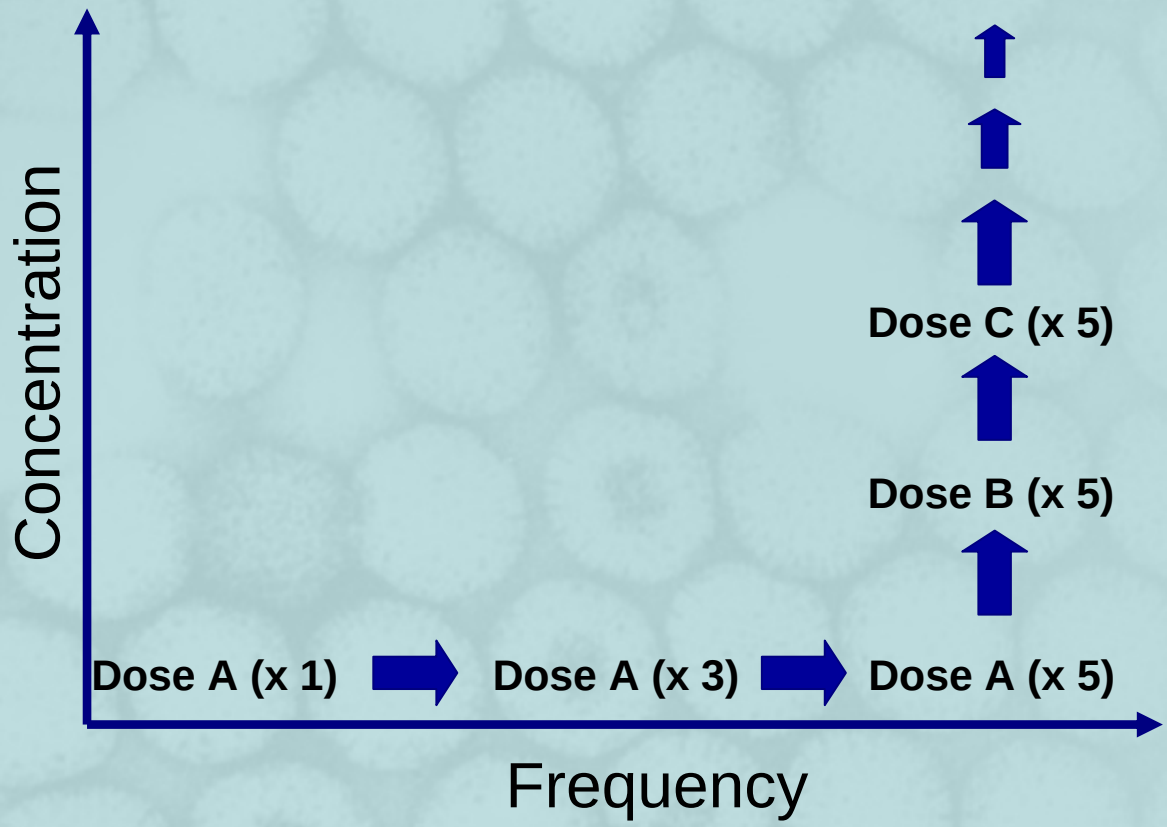
UK dose escalation – Phase I component



- Study designed to look at effect of increasing frequency and dose
- Allowed multiple administrations (4 week cycle)
- Expansion at top dose to better measure efficacy

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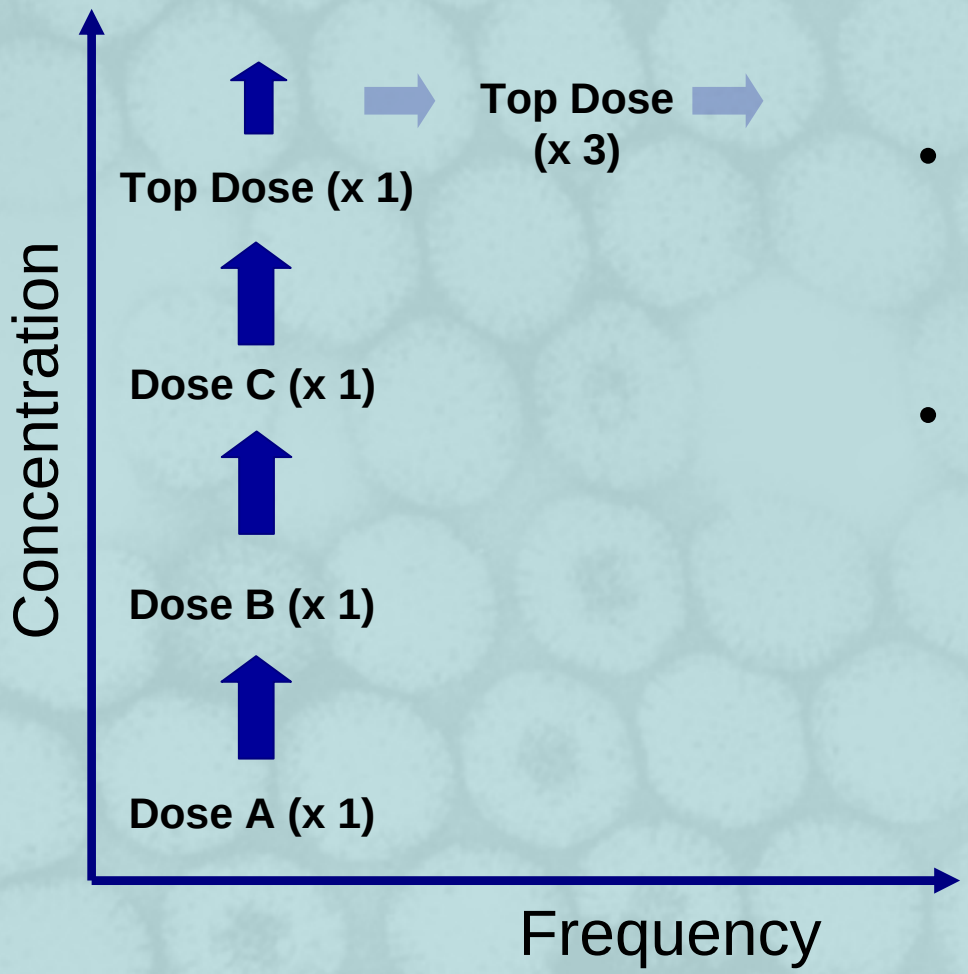
US dose escalation – Phase I



- Study designed to look at increasing dose only
- Single cycle only (until sufficient data generated from UK study)
- No expansion at top dose

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Different jurisdictional issues

- MHRA
  - Pro – early allowance to look at repeat administration and multiple cycles
  - Con – concern with shed required first cohorts to be treated in hospital in negative pressure rooms resulting in slow accrual and added cost
- FDA
  - Pro – realistic view of the risk posed by shed of a naturally occurring virus allowed patients to be treated in out-patient care resulting in rapid enrolment
  - Pro - allowed early interaction with the Agency
  - Con – initial concerns with risk of repeat administration required first cohorts to receive single administration only
- By concurrently running the studies, it was believed that the transition into Phase II studies in multiple jurisdictions would be expedited

REOLYSIN clinical overview - systemic monotherapy

Trial	Patient Population	Tumour Response
Phase I systemic administration (UK)	Late-stage or advanced cancer patients who have failed all other therapies. (N=33)	Responses noted in several tumor types - Colorectal cancer 2 patients : Stable Disease at 3 and 6 months; CEA tumor marker reduction of 27% and 60% - Metastatic prostate cancer one patient: Stable disease at 4 months 50% decrease in PSA. Biopsy lymph node – EM: Viral replication. Pathology - Necrosis - Metastatic bladder cancer one patient: Stable disease at 4 months. Minor tumor response (24% tumor reduction) in metastatic lesion (lymph node); patient later reported as disease free post surgery (pPR). - Pancreatic cancer one patient: Stable disease at 4 months. - NSC Lung Cancer one patient: Stable Disease at 4 months.
Phase I systemic administration (US)	Late-stage or advanced cancer patients who have failed all other therapies. (N=18)	44% showed stable disease or better One partial response in progressive breast cancer

REOLYSIN clinical overview – Phase II program

Monotherapy Phase II Program
 	
Program status – ongoing
	▪ US: recurrent sarcoma metastatic to lung (ongoing)
	  ▪ Trial has met initial criteria to proceed to full enrolment
	  ▪ One patient stable for >6 months
	▪ NCI: melanoma and ovarian cancer
	  ▪ Trials received FDA approval, enrolment to begin Q1 2008

These studies employ the recommended dose from the UK study (ie 5 injections/week on a 4 week cycle)

Phase II monotherapy program is currently exclusively conducted in the US

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REOLYSIN clinical overview – Phase I/II program

Phase I/II Drug Combination Program Program status - ongoing	Combination: UK: Phase II low dose radiation including head/neck (ongoing) Combinations with cytotoxics (dose escalation ongoing) ▪ Gemcitabine ▪ Docetaxel ▪ Carboplatin/paclitaxel REOLYSIN + cyclophosphamide (MHRA approval received)

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Imaging, tumor markers and histopathology

- Phase I program suggested that conventional imaging (CT) was inadequate to measure responses caused by REOLYSIN
  - Demonstrable tumor marker responses by CEA, PSA, and CA199 without 2D changes in CT
  - Histopathologic response in post-treatment biopsies and surgical specimens without 2D changes in CT

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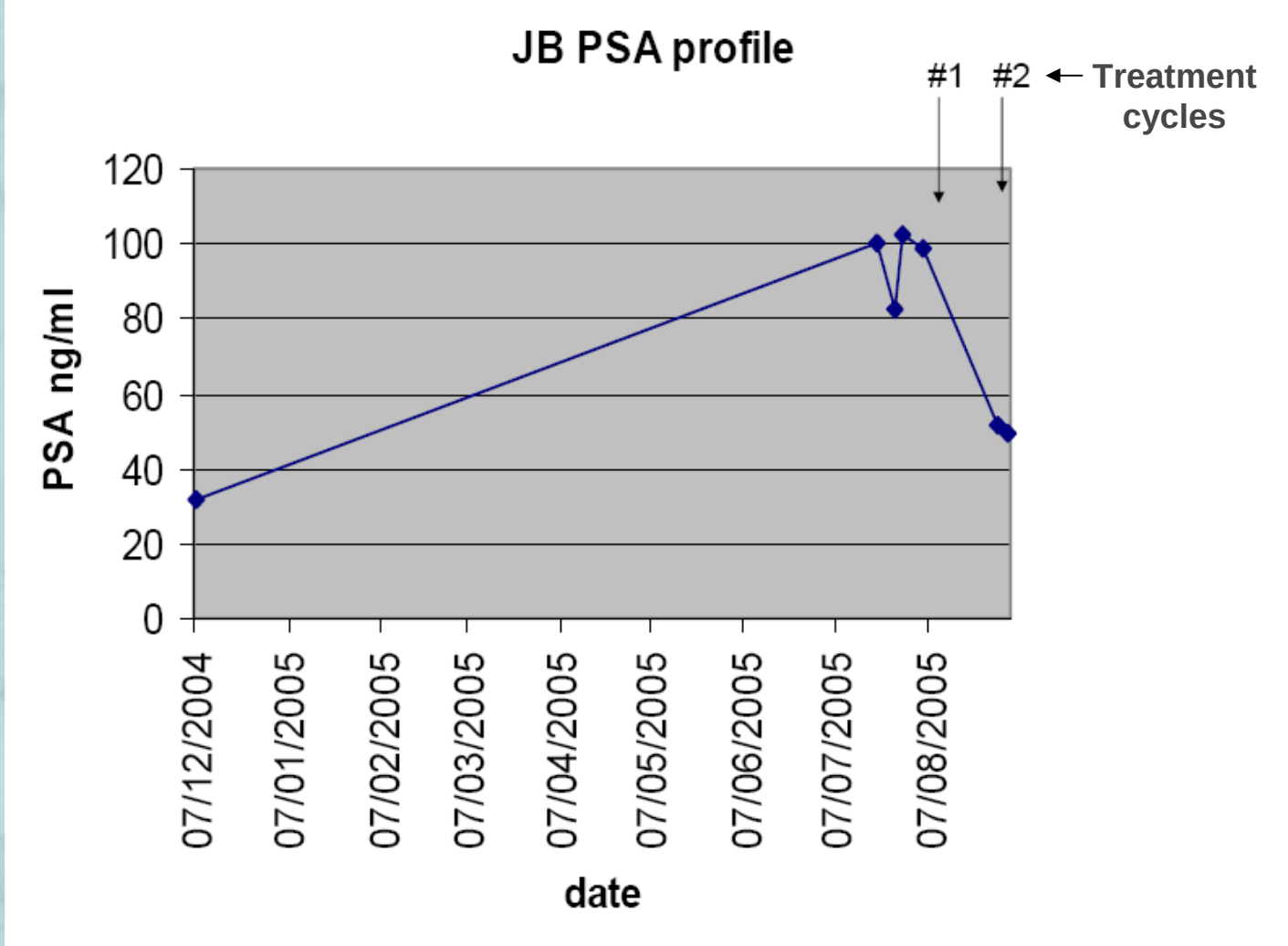
Example - PSA response – patient JB



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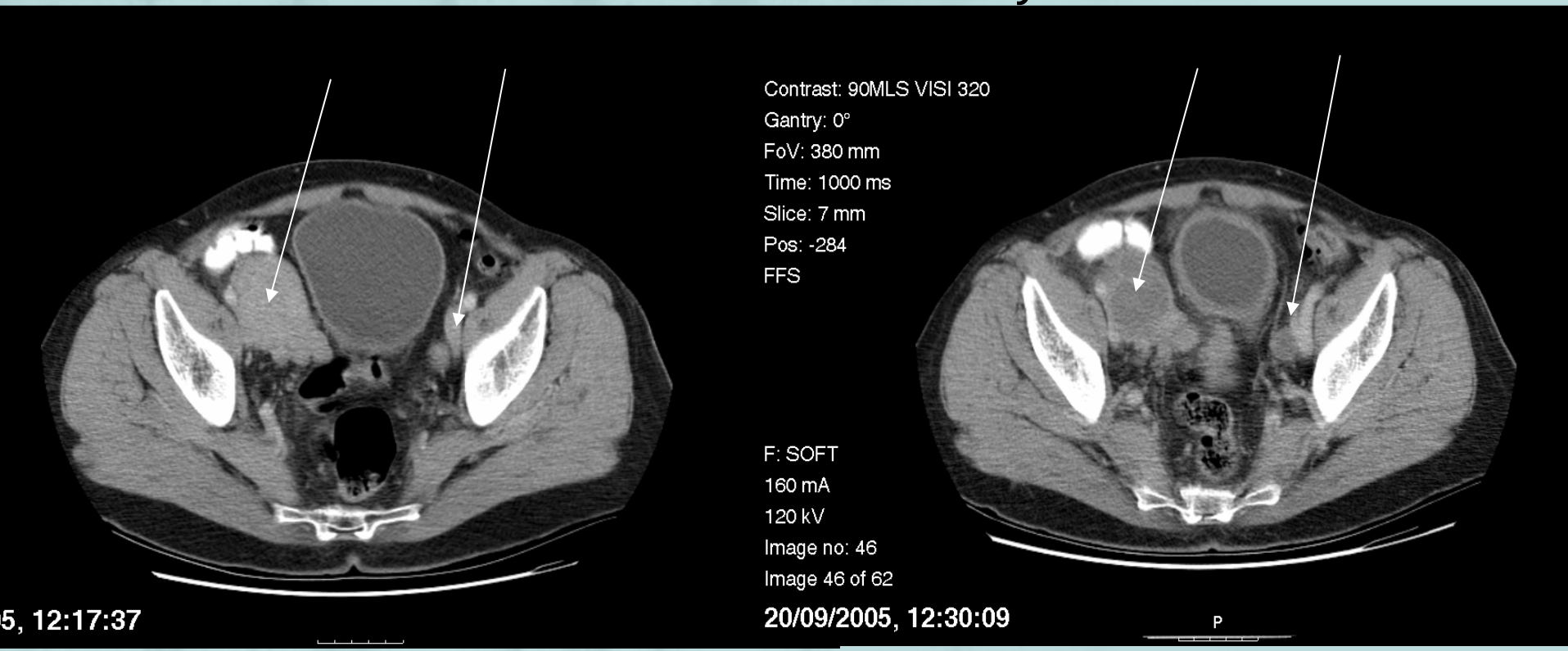
CT Scan – patient JB

Pre-treatment

Post 2 cycles of REOLYSIN®



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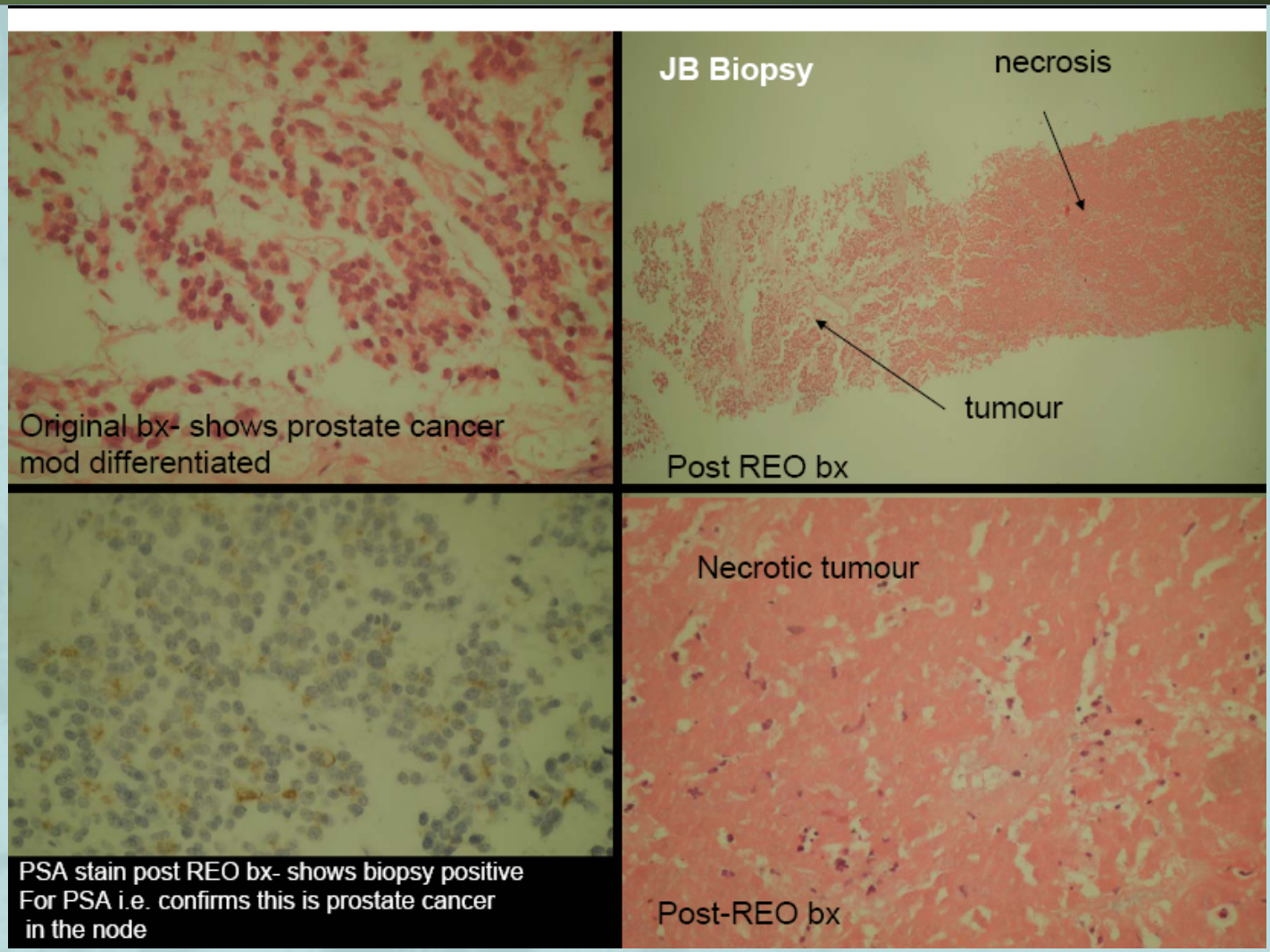
Metastatic prostate patient's histology – patient JB



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Phase II program – addition of functional imaging

- In response to imaging concerns the Company introduced the use of PET/CT into Phase II programs. Introduction of this imaging modality is already bearing fruit:
  - Phase II sarcoma study has demonstrated that a patient with 6 month SD (CT RECIST) has metabolically inert disease by PET and study has moved to full enrolment (enrolment ongoing)

REOLYSIN: lessons and issues

- Key strategic decisions
- Impact of regulatory interactions
- Financial considerations: projected costs vs. reality
- Lessons learned

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