GlobeImmune

Recombinant DNA Advisory Committee Meeting
June 8-9, 2004

Discussion of Human Gene Transfer Protocol #0404-641 entitled: *A phase I open label, non-randomized, dose-escalation, multi-center, therapeutic trial of the safety, immunogenicity and efficacy of GI-4000, an inactivated recombinant Saccharomyces cerevisiae immunotherapeutic expressing three different mutations of the Ras oncoprotein, in patients with solid tumors expressing mutations in Ras*

TARGETED MOLECULAR IMMUNOTHERAPY

Protocol #0404-641 (GI-4000-01)

- Bert O'Neil, M. D., UNC-CH, Principal Investigator
- Timothy C. Rodell, M. D., GlobeImmune CEO
  - Medical and Safety Monitor
- Richard Duke, Ph. D., Founding Scientist
- Alex Franzusoff, Ph. D., Founding Scientist, VP-Research
- John Ferraro, CCRA, Manager, Clinical Operations

GlobeImmune

- Colorado based immunotherapy company targeting cancer and chronic viral diseases
- Recombinant yeast based immunotherapy platform
- Cancer
  - GI-4000 – mutant Ras - colorectal, pancreatic, NSCLC, ovarian
  - GI-3000 – EGFR – glioblastoma, NSCLC
  - GI-6000 – Muc1 – breast, pancreatic
  - GI-7000 – Mart1 – melanoma
- Viral
  - GI-2010 – Gag – HIV/AIDS
  - GI-5000 – core/NS3 - HCV

GlobeImmune platform

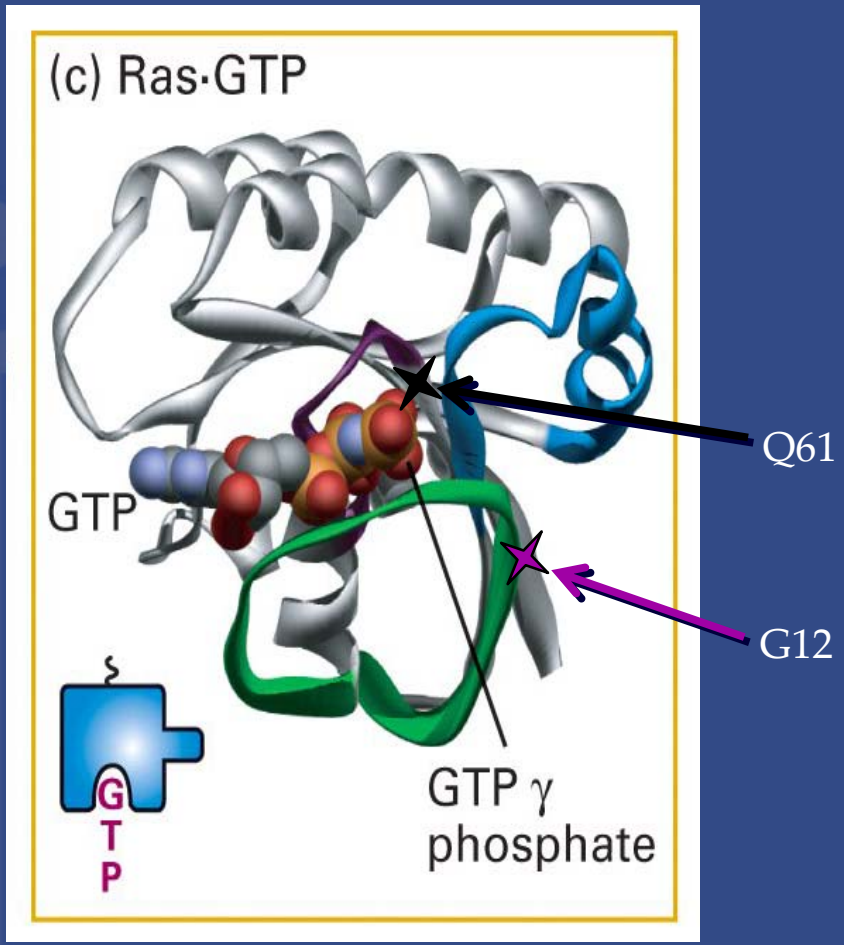
- Heat killed recombinant *S. cerevisiae* transfected with gene for target antigen
  - Produce precise amount of target protein
  - Receptor mediated uptake by antigen presenting cells
  - Activation of antigen presenting cells
  - Elicit potent antigen-specific T cell responses
  - Not neutralized
  - Non-toxic in preclinical studies
  - Potential for multiple antigen delivery
  - Easy and inexpensive manufacturing

Ras mutations as cancer targets

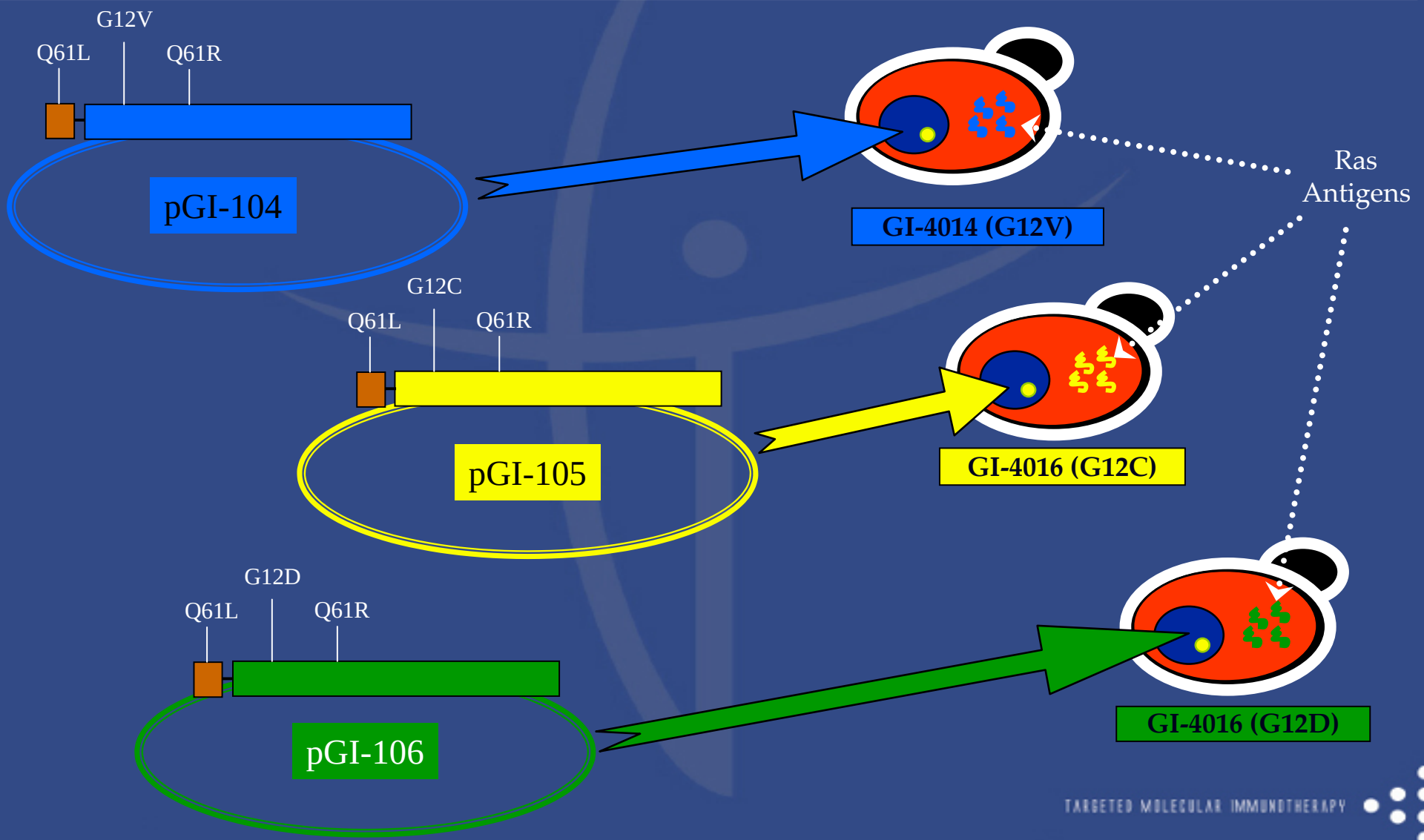
- Intracellular signaling protein
- Second messenger in EGFR pathway
- Activating mutations at “hotspots” cause constitutive activation
- Activating mutations are sufficient for carcinogenesis
  - Second mutations not required
- Most commonly mutated oncogene in human cancer

Frequency of Ras mutations

- Codon 12
  - Pancreatic – 90% (G12D,V)
  - Colorectal – 34% (G12D,V,C)
  - NSCLC – 27% (G12C,V)
  - Ovarian – 24% (G12D,V)
- Codon 13
  - Pancreatic – 2%
  - Colorectal – 12%
  - NSCLC – 5%
- Codon 61
  - Colorectal – 4%
  - NSCLC – 7%



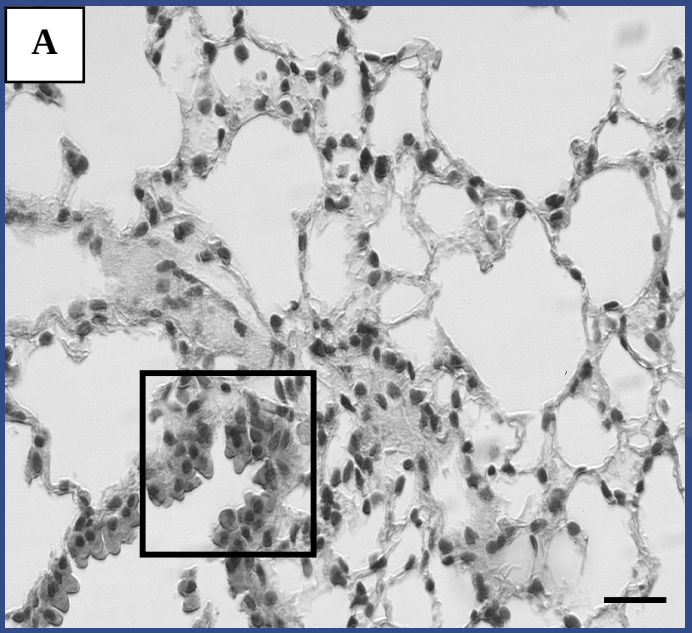
GI-4000 series



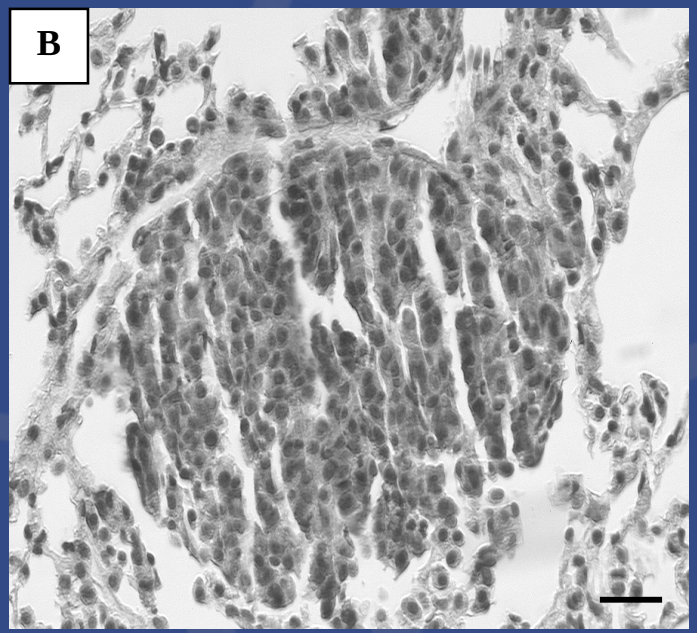
GI-4001 in mouse lung adenocarcinoma

- Urethane treated A/J mice develop spontaneous lung adenomas/adenocarcinomas associated with K-ras 61 mutations
- Ras-61 IT (GI-4001) administered on days 7, 14, 35 and 56
- Sacrifice on day 100 and tumors sized and counted

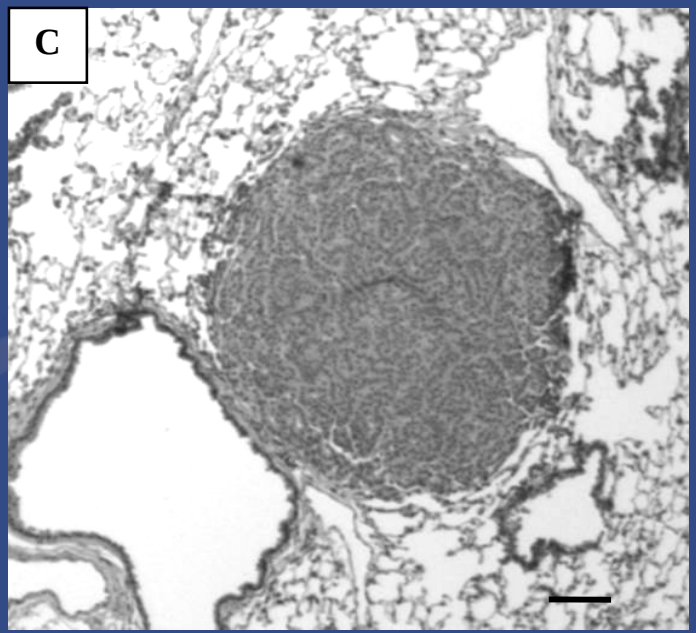
Tumor progression after urethane induction



Hyperplasia - 2 weeks



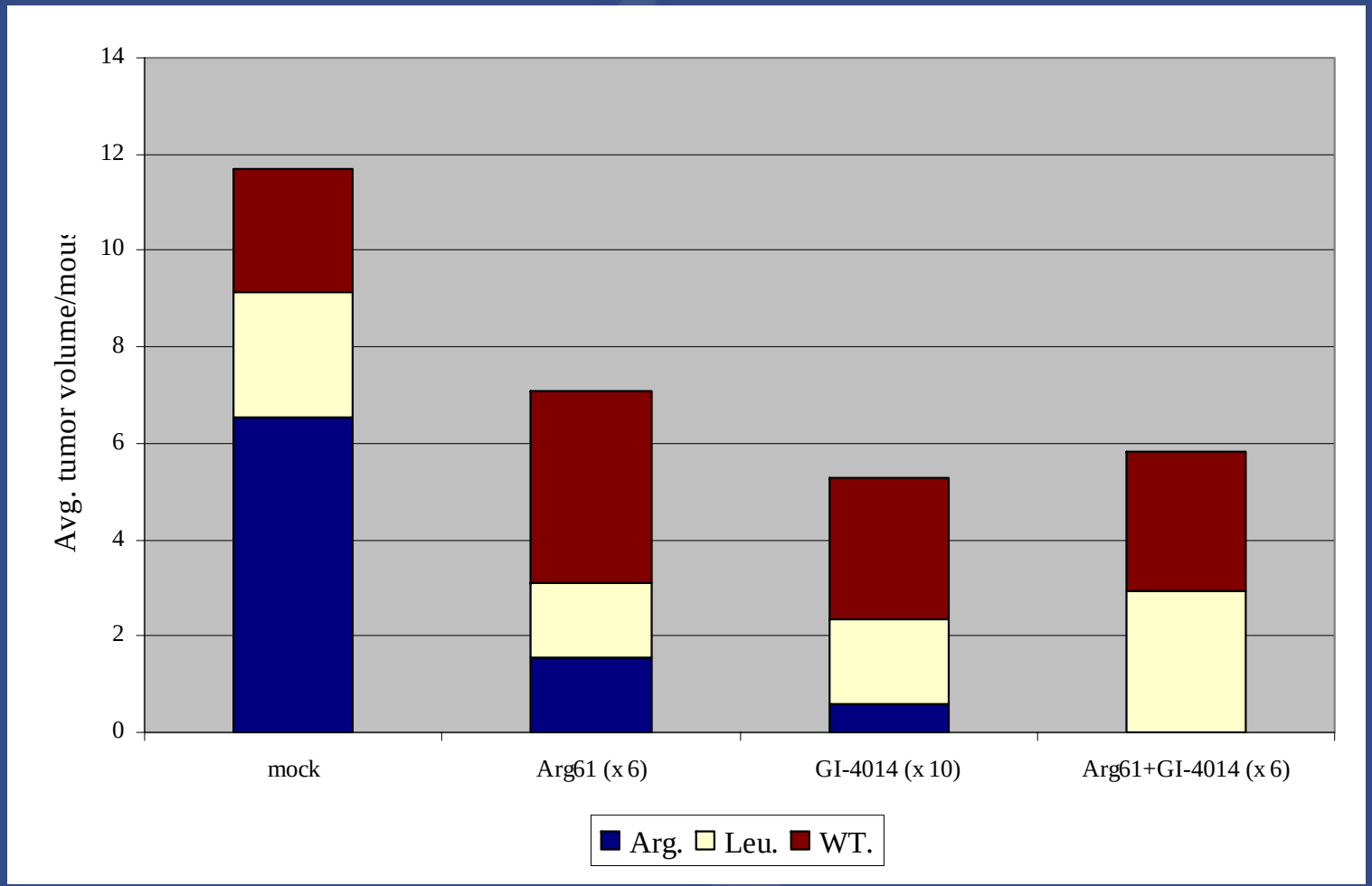
Microadenoma - 5 weeks



Adenoma - 16 weeks

Scale bar: 10μm panels A and B; 50 μm panel C
Figure provided by Drs. Kisley, Nield and Malkinson

Tumor remission following GI-4000 administration



GI-4000 development

- Pre-IND teleconference w/OTCGT January 6
- Two tox lots of GI-4014, -4015 and -4016 produced
- Pivotal GLP toxicity study in rabbits
- Clinical lots produced and vialed
- IND submitted April 04
- IND active May 04
- Four Phase 1 trial sites identified and protocol submitted to IRBs

GI-4000 Phase 1

- Patients with Stage III & IV colorectal, pancreatic, NSCLC
- Open label, dose escalation, 4 doses
- Four centers
  - UNC-CH, Duke, FHCRC, U. S. Oncology/RMCC
- Sequence tumor for Ras codon 12 or 61 mutation
- Weekly s.c. administration for 5 doses – 84 day f/u
- Endpoints
  - Safety
  - *In vitro* cellular immunology
  - Disease progression (RECIST)

Issues raised during RAC review

- General
  - Rationale for targeting mutated Ras
  - Is this the first protocol using same vector for prime/boost?
- Chemistry, Manufacturing, Controls
  - Heat inactivation of yeast
  - Nomenclature (GI-4000 = GI-4014, 4015, 4016)
- Non-clinical
  - Comparison with other therapies

Issues raised during RAC review

- Clinical
  - Enrollment of end stage patients and integrity of their immune systems
  - Potential for complement activation
  - Potential for germ line mutations in Ras
  - Potential for mix up of three products
  - Dose escalation strategy with 3 products/statistical issues w/ 3 products
  - Quality control with < 3 patients at each site

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Issues raised during RAC review

- Informed consent
  - Autopsy request
  - Reading level
  - Payments to investigators/financial interest in GlobeImmune
  - Three products vs. one
  - Explicit inclusion of pregnancy test
  - Withholding of medications for skin test
  - Need for biopsy
  - Withholding of chemotherapy

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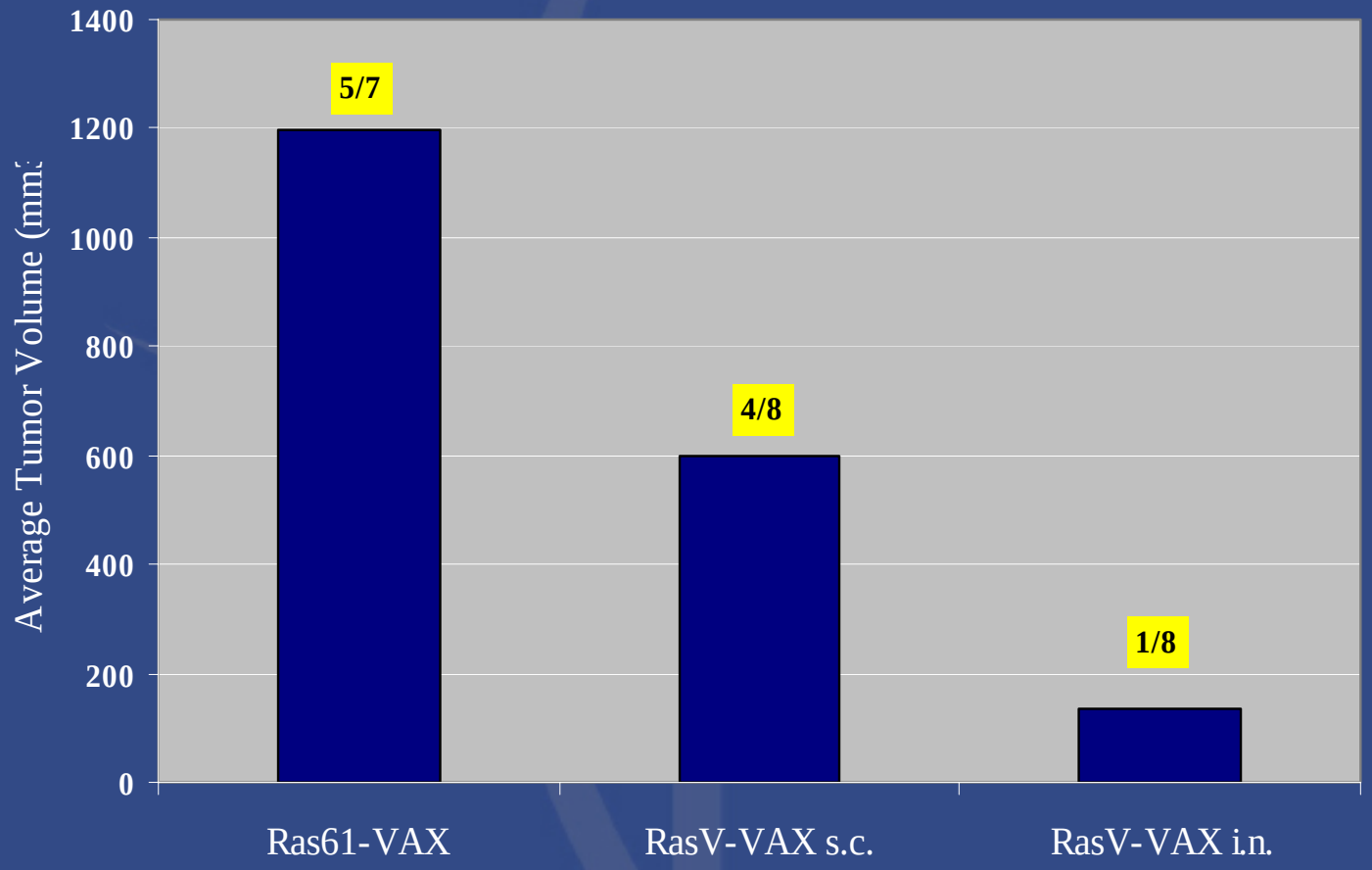
Human tumor sequencing

- 25 NSCLCs sequenced from paraffin blocks
- 6/25 with mutations at codon 12
- All but one contained in GI-4000 series

GI-4000 series validation

- CMT64 cells from spontaneous mouse lung adenocarcinoma
- Endogenous mutation K-Ras codon G12V
- Ras GI-4001 or GI-4003 (Ras G12V) on days 1, 8, 22
- CMT64 cells implanted s.c. day 29
- Sacrifice and measure tumor size and frequency

GI-4000 protection is antigen specific



CMT64 cells implanted s.c.
Above bar is shown # mice with tumors/total number at day 30 after challenge

GI-4000 dose/frequency in pre-existing lung tumors