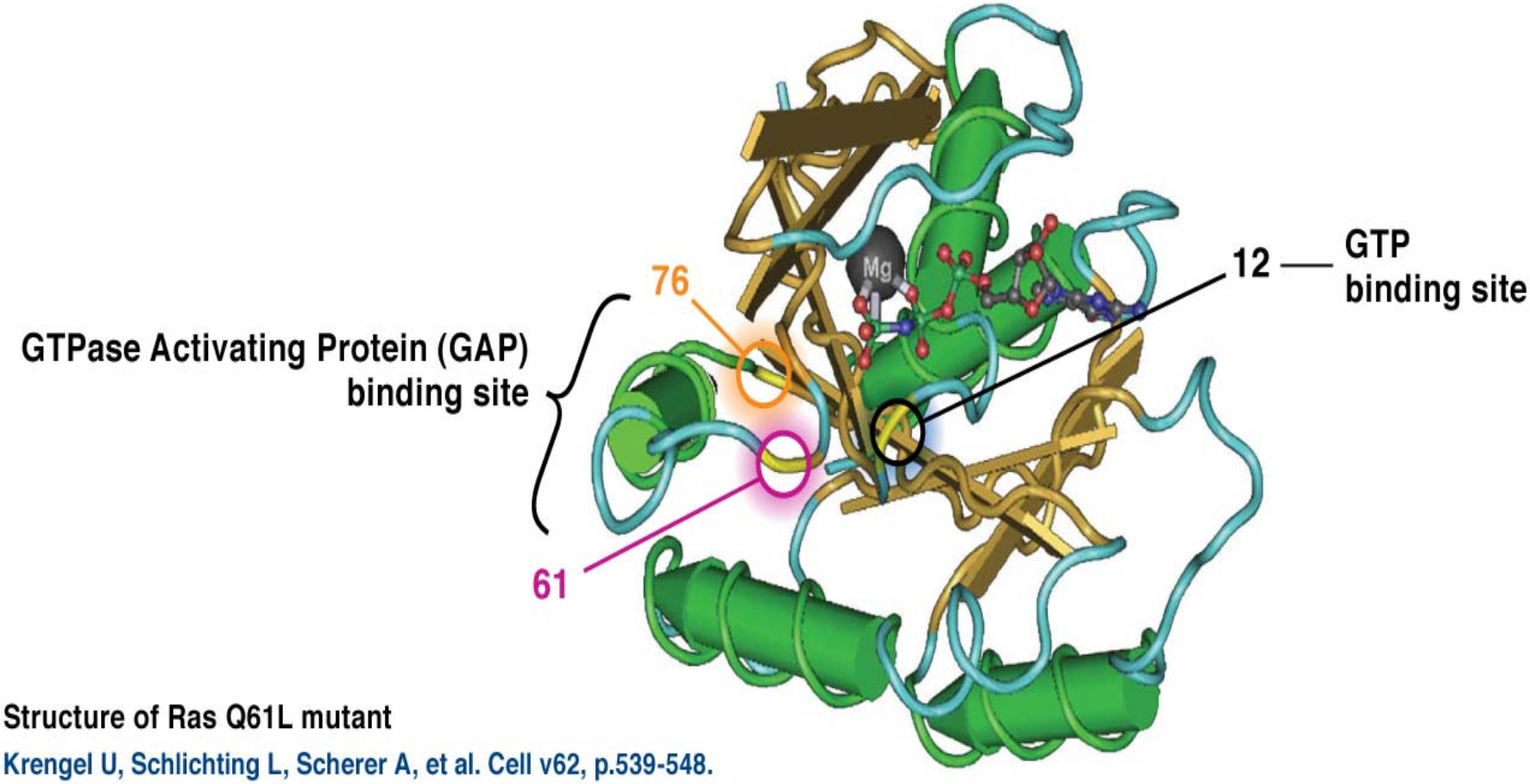
GlobeImmune

FDA ODAC meeting
December 2008

TARGETED MOLECULAR IMMUNOTHERAPY

Mutations at 12, 13, 61 & 76 affect Ras function



Structure of Ras Q61L mutant

Krengel U, Schlichting L, Scherer A, et al. Cell v62, p.539-548.

Genotyping techniques & limitations

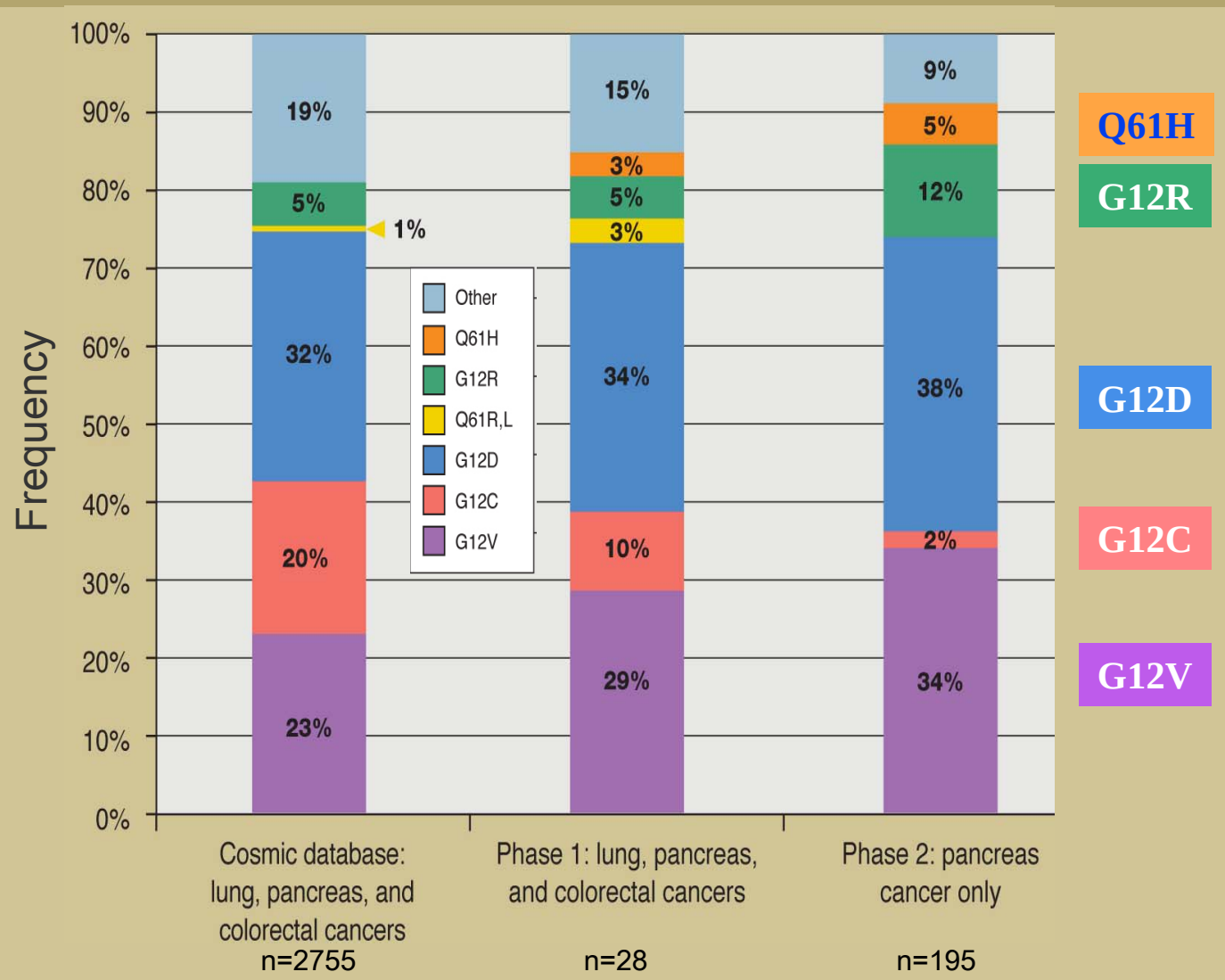
- "Gold standard" double stranded sequencing
  - Optimization for improving sensitivity & accuracy (e.g. PNA)
    - Remove interference from wild type *ras* sequence
    - Reduces risk of false negatives
- Other commercially available methods
  - More streamlined methods, amenable to kit production
  - Higher risk of false positives
  - Higher risk of false negatives
- Breadth of *ras* mutations to be addressed
  - How to reduce artifactual false negatives
    - Full range of exon 2 mutations (codon 12, 13, 14)
    - Exon 3 transforming mutations (codons 59, 61, 76)

Tumor genotyping summary

Tumor source	Tumor type	# samples analyzed	% *ras* mutant
Non-trial patients (analyzed without PNA)	pancreas	41	51%
	NSCLC	25	28%
Phase 1 trial subjects (analyzed without PNA)	pancreas	34	71%
	colorectal	86	43%
	NSCLC	32	22%
Phase 2 trial subjects (analyzed with PNA)	pancreas	197	86%

Total # samples analyzed to date: 415

ras mutation prevalence



ras genotyping – conclusions

- Promise for predicting outcomes in cancer therapy
- Implications of false positives
  - Withholding potentially beneficial therapies
- Implications of false negatives
  - Administration of therapies unlikely to confer benefit
- Breadth of mutation coverage is critical

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