

Jim Brown - Role of Evol. Biology in Drug Discovery

Showered cam survive on caviar: oysters as a grad. student

practical importance of evol. analysis

throughout all branches of tree - organism critical to human health

1. Evolutionary biology pays
2. Origin of drug resistant aa-tran
3. Lateral transfer

Glaro-Smith - Klini

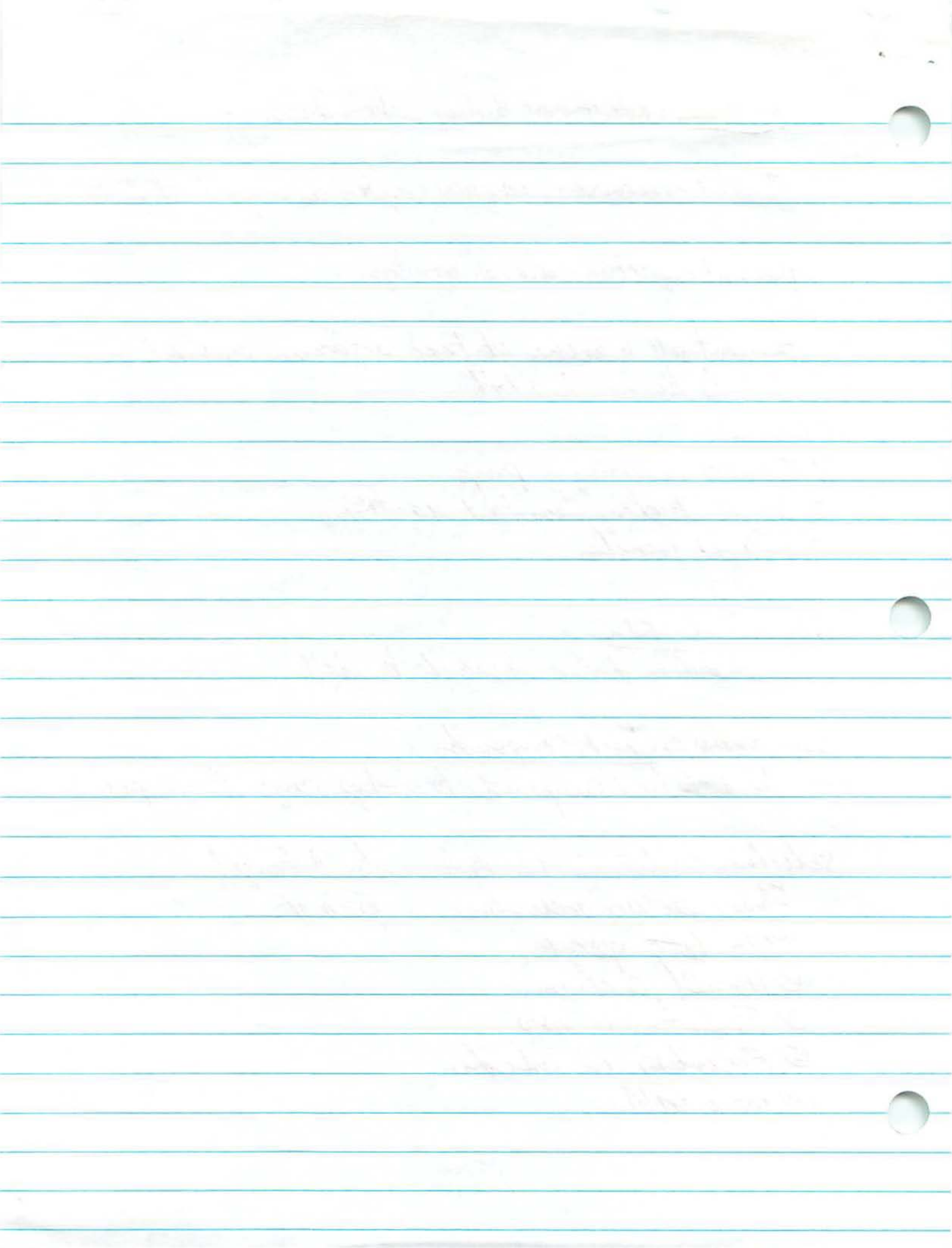
- 4 billion dollar research budget

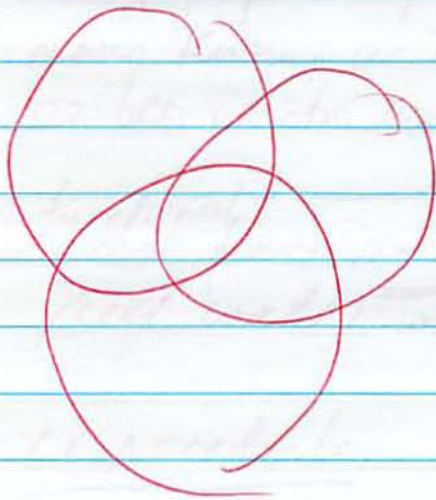
New antimicrobial compounds

- hard to find compounds to bridge range of compounds

Selection criteria for Antimicrobial targets

- ① Broad spectrum occurrence in gram +/-
- ② Bacterial specific
- ③ Novel action
- ④ Essential in vivo
- ⑤ Essential in vitro
- ⑥ Inhibitable





① in silico analysis

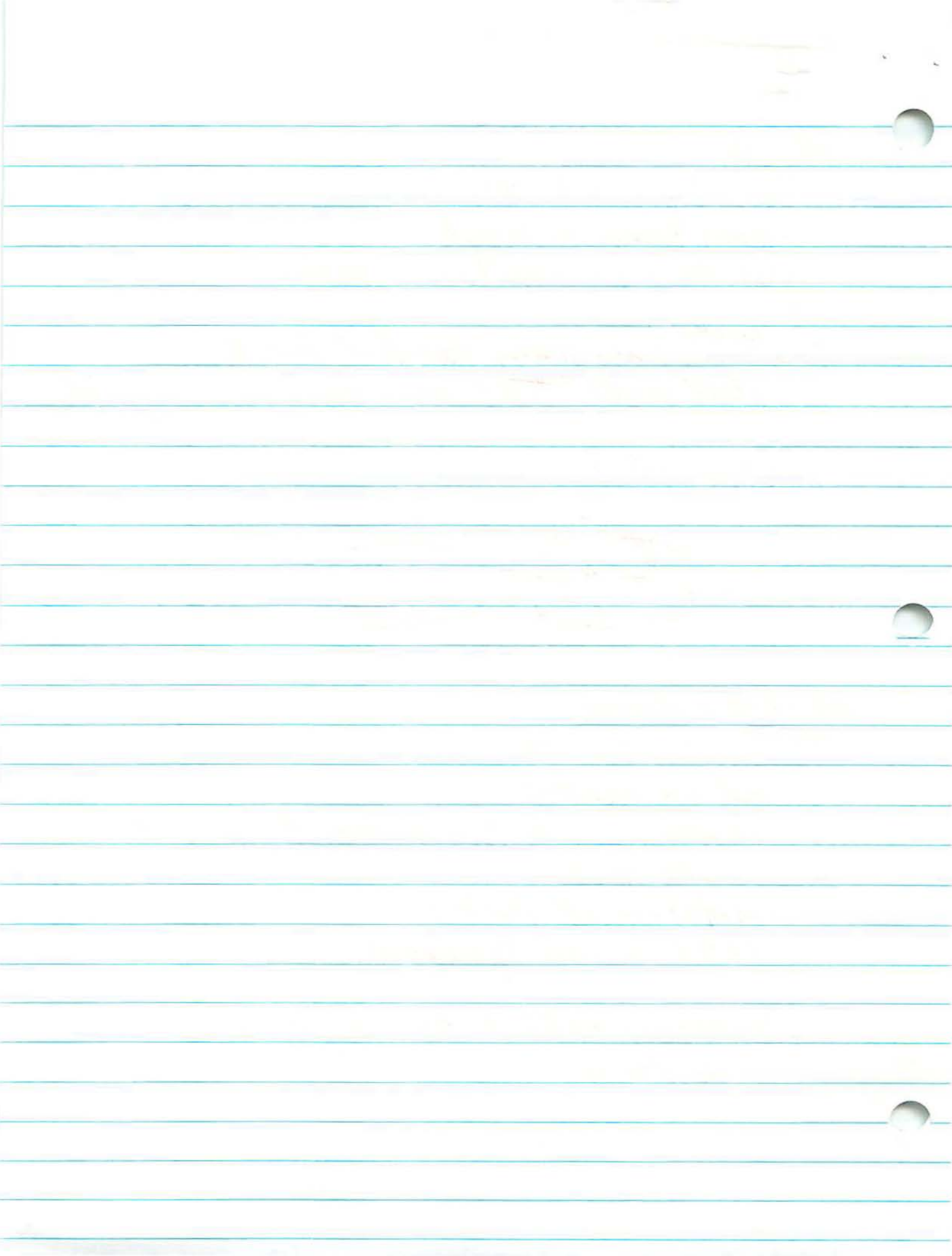
- ① must be in X genomes
- ② ideally single copy
- ③ low homology to mammals
- ④ complete sequences available

② Issues in prioritization:

- ① need genomes - bat
- ② need genomes - human / mouse
- ③ data source fragmented

③ Analysis

- N x N blastp
- trees

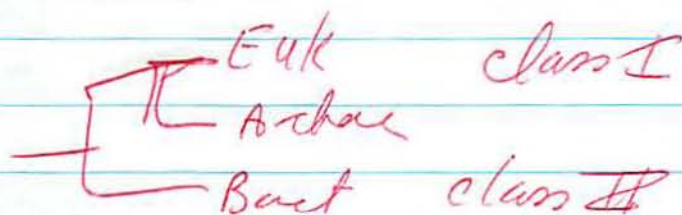


Results

- ~500 high priority ORFs
- many known as targets
- 122 ORFs in-vitro essential in *S. pneumoniae*

functional!
Some areas have many essential targets
(cell wall) while others have few (signalling)

Hm 6 Cat - redundancy

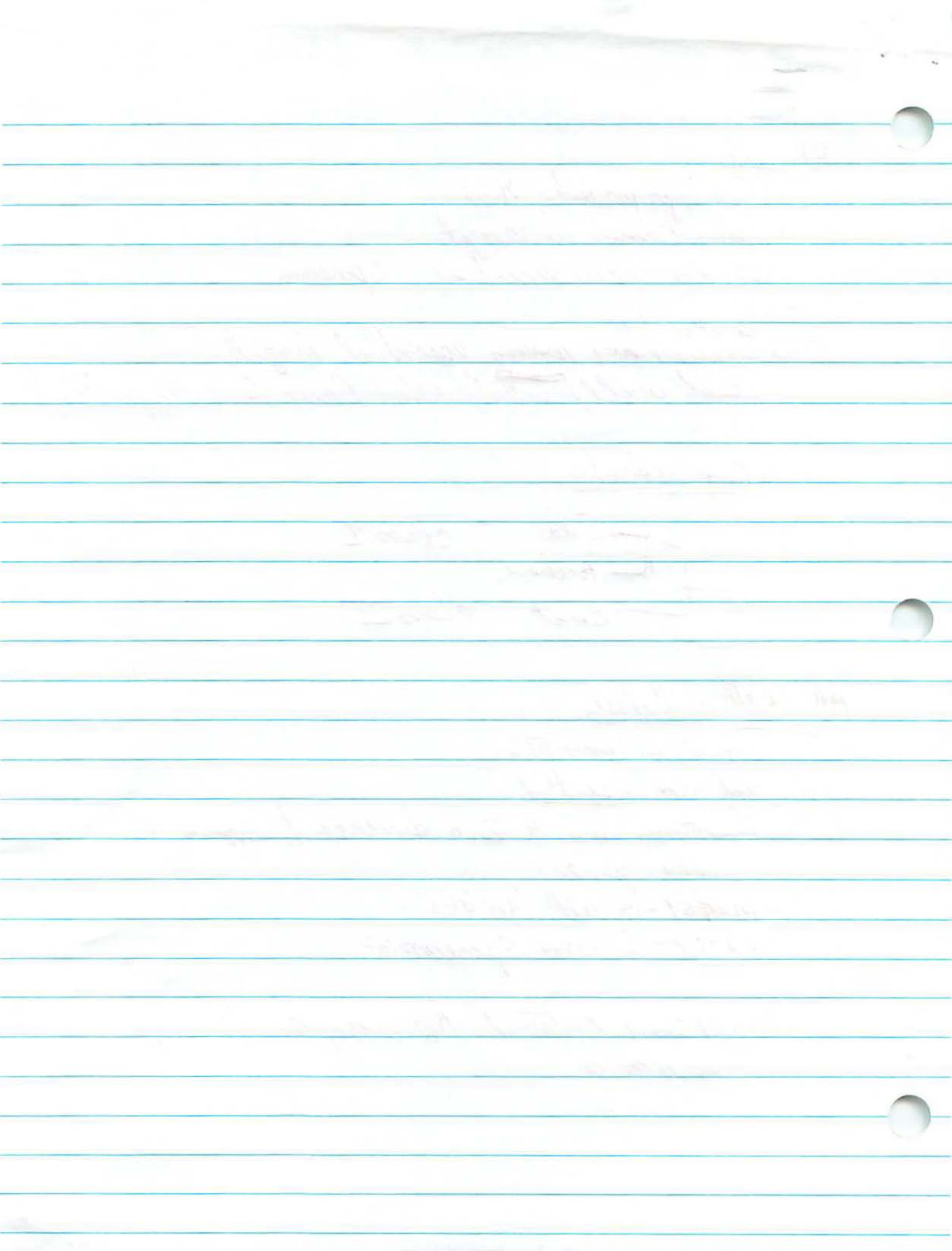


AA. tRNA synthetases

- critical in translation
- all are essential
- resistance due to 2nd divergent copies of some genes
- mufs1 - in all low GCs
- mufs2 - in some *S. pneumoniae*

Thinks some natural Ab may be driving resistance

Jan



MetsZ - in anthrax

Then looked at other aa-trpA syn. targets

"Bactroban cream"

- Mupirocin inhibits IleS

- Staph aureus has some resistance

- highest resistance due to plasmid-borne

- Some have IleS

- also in anthrax

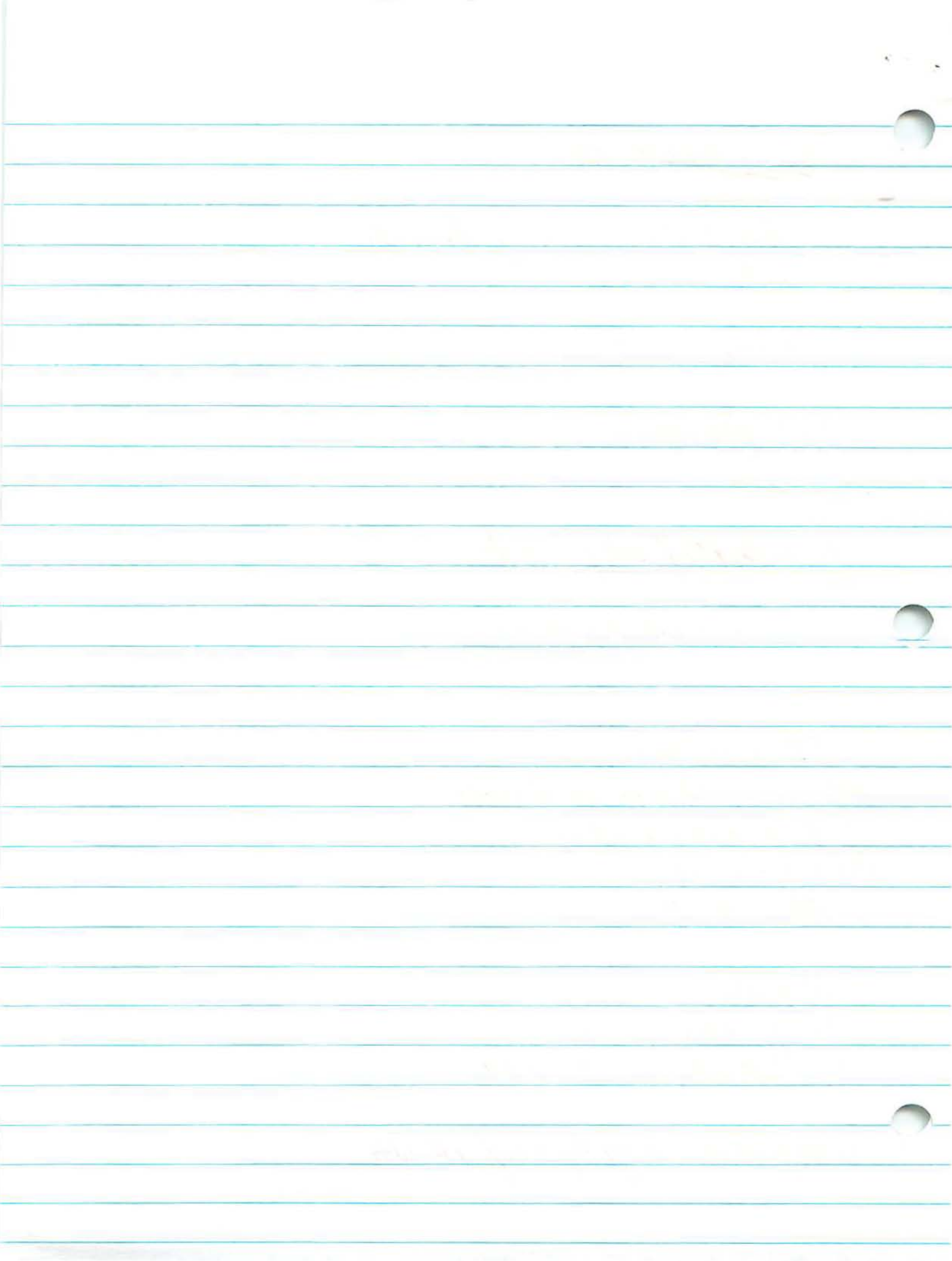
PanK - regulates CoA synthesis

- most bact. have bPanK

- most euk. have ePanK

- Bacan + Staph have epanK

Suggests anthrax may be reservoir of genetic variation.



HGT + tree of life

- GST } clearly some transfer
- GST }

- Is the tree a net

blast = phylogeny

Concatenated alignments

- homoplasy $\neq$ homology

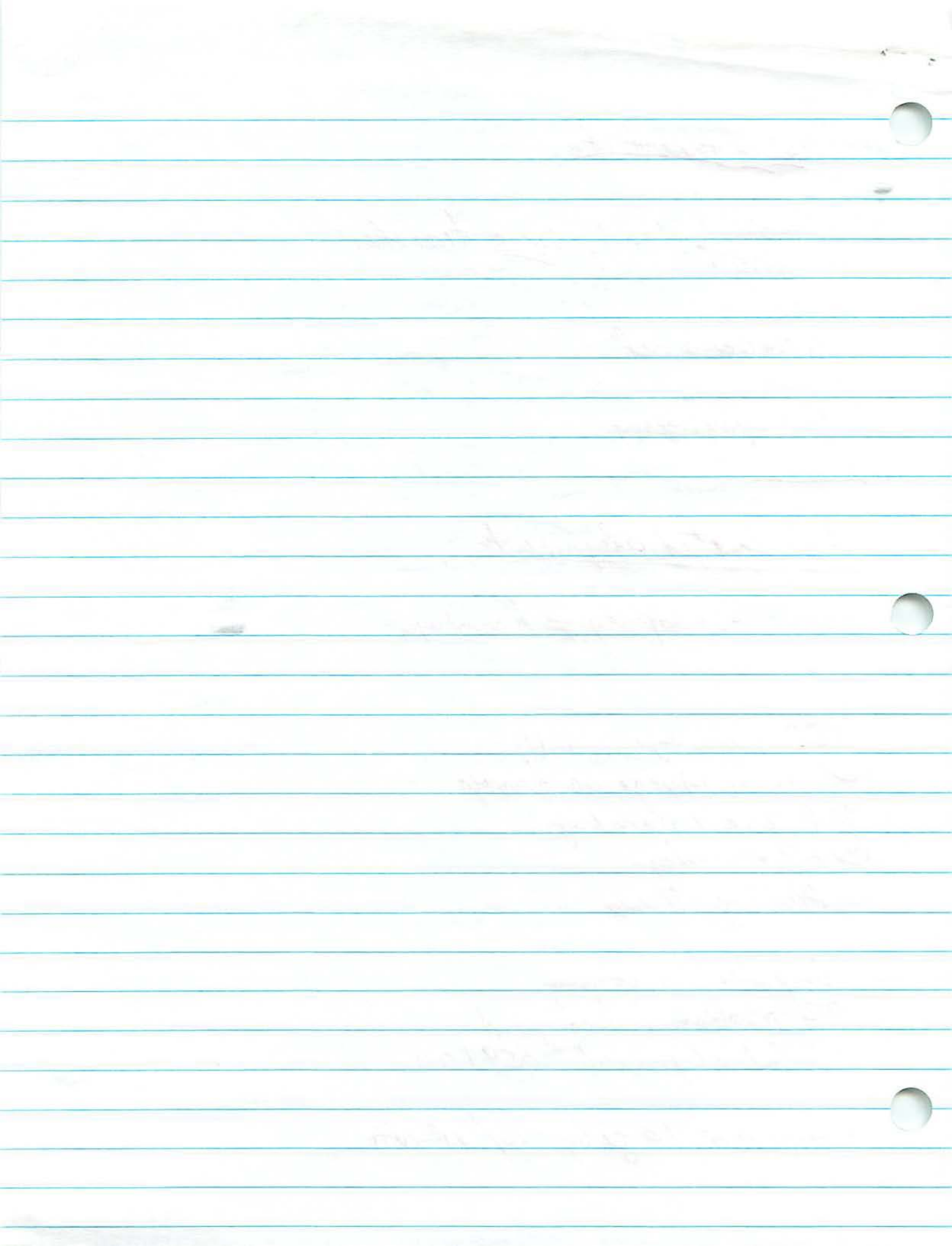
- ① ID homologs in all
- ② using Mycog as driver
- ③ Filter out paralogs
- ④ Edit + align
- ⑤ Phylog. trees

- 65 proteins in common

- 23 proteins looked good

- total alignment = 6591 aa.

- congruent / largely - w/ rRNA



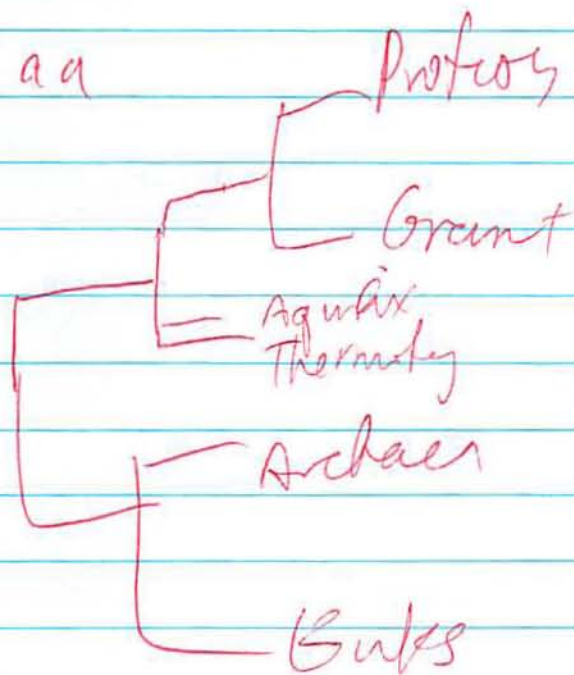
rooting different that dup. genes



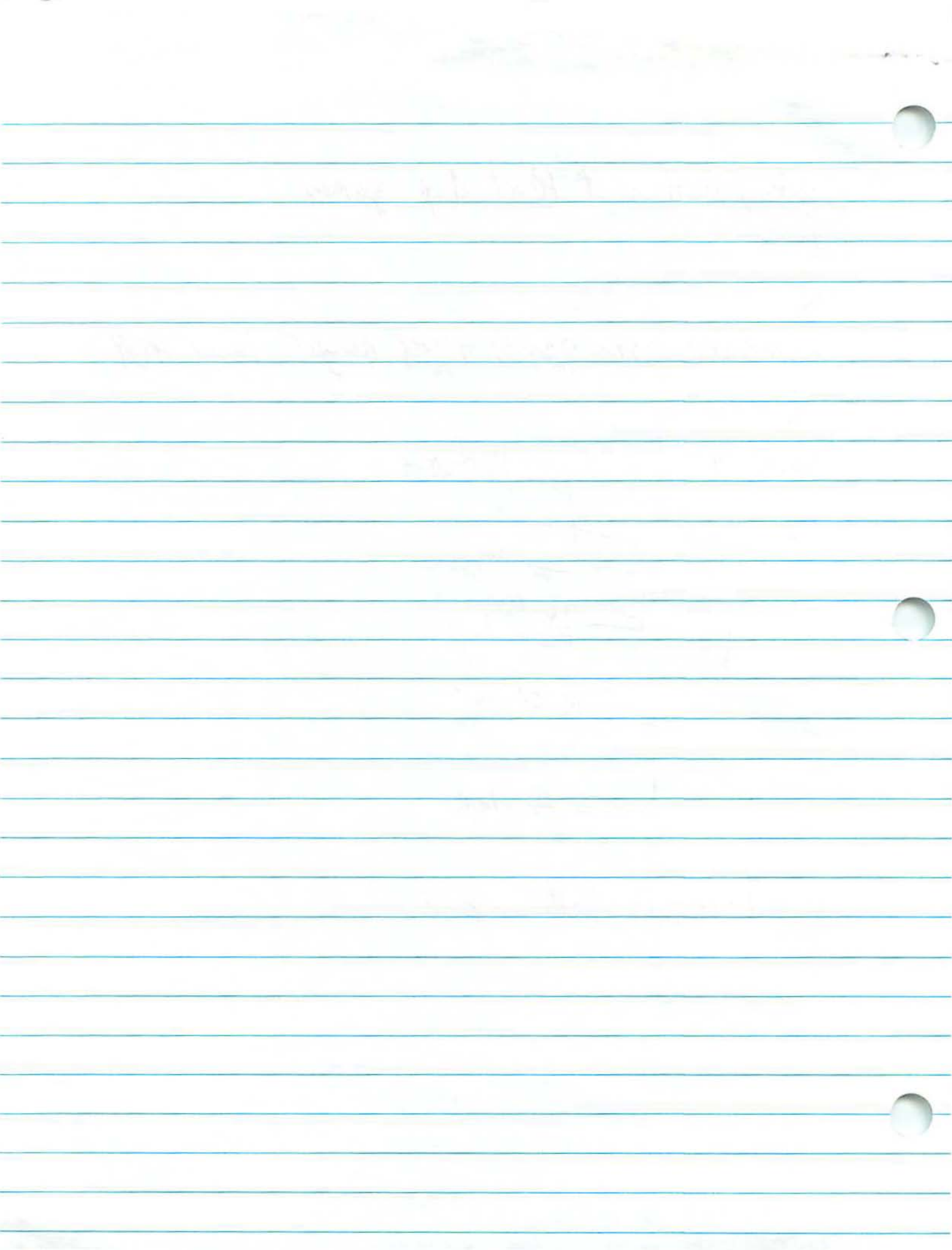
removed some genes that might have HGT



3824 aa



large data sets = better signal



Evol Biology - why should Pharma care

① Drug discovery is based on guessing f/d

② Popgen

③ Classification of ~~genes~~ targets

④ Gene association

⑤ Garbage in is garbage out

what is true for E. coli is also true for
elephant only more so.

J. Monod

1. Introduction

2. Background

3. Methodology

4. Results

5. Discussion

6. Conclusion

7. References

8. Appendix