Direction of DBA Research

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Camp Sunshine

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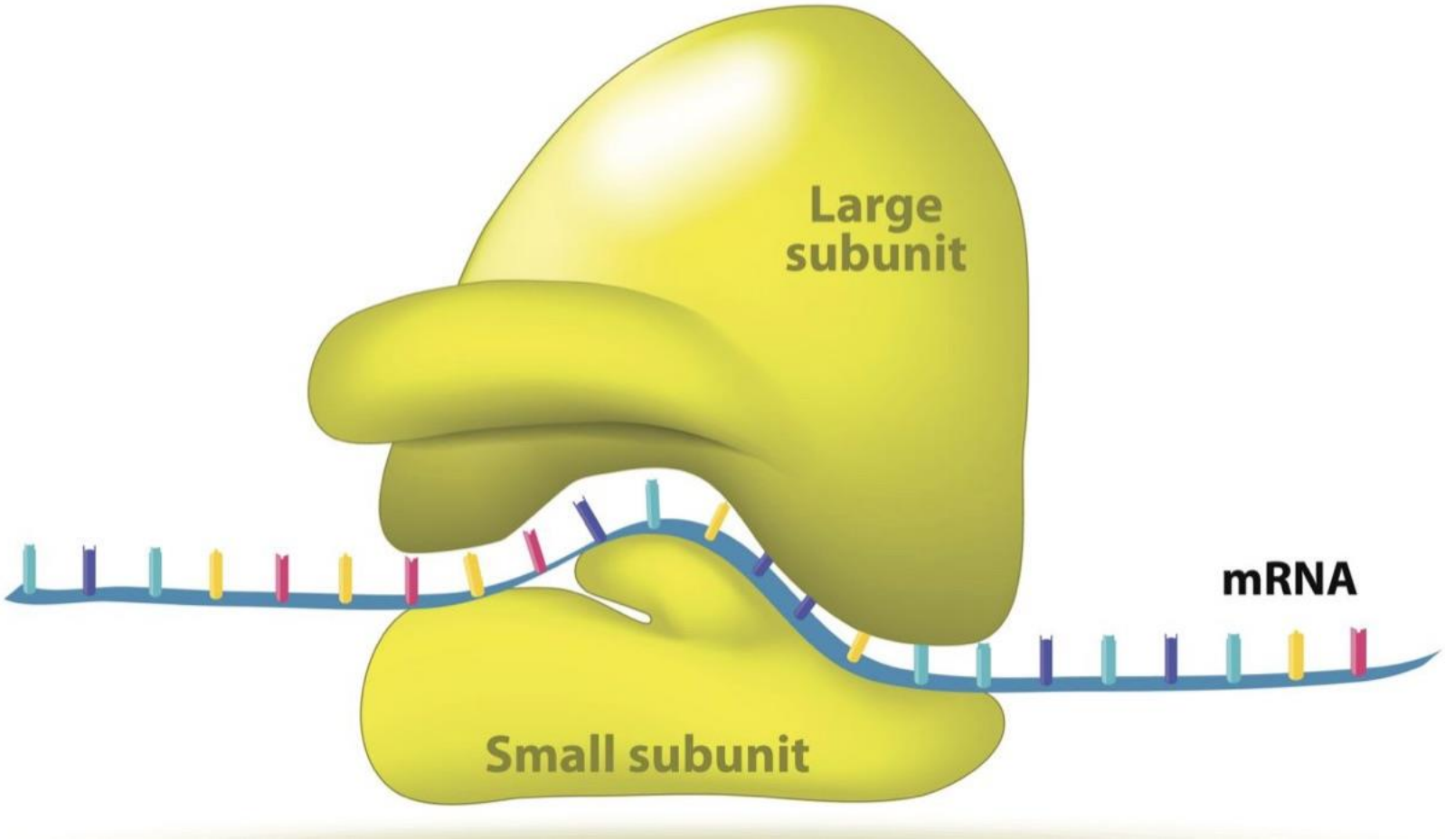
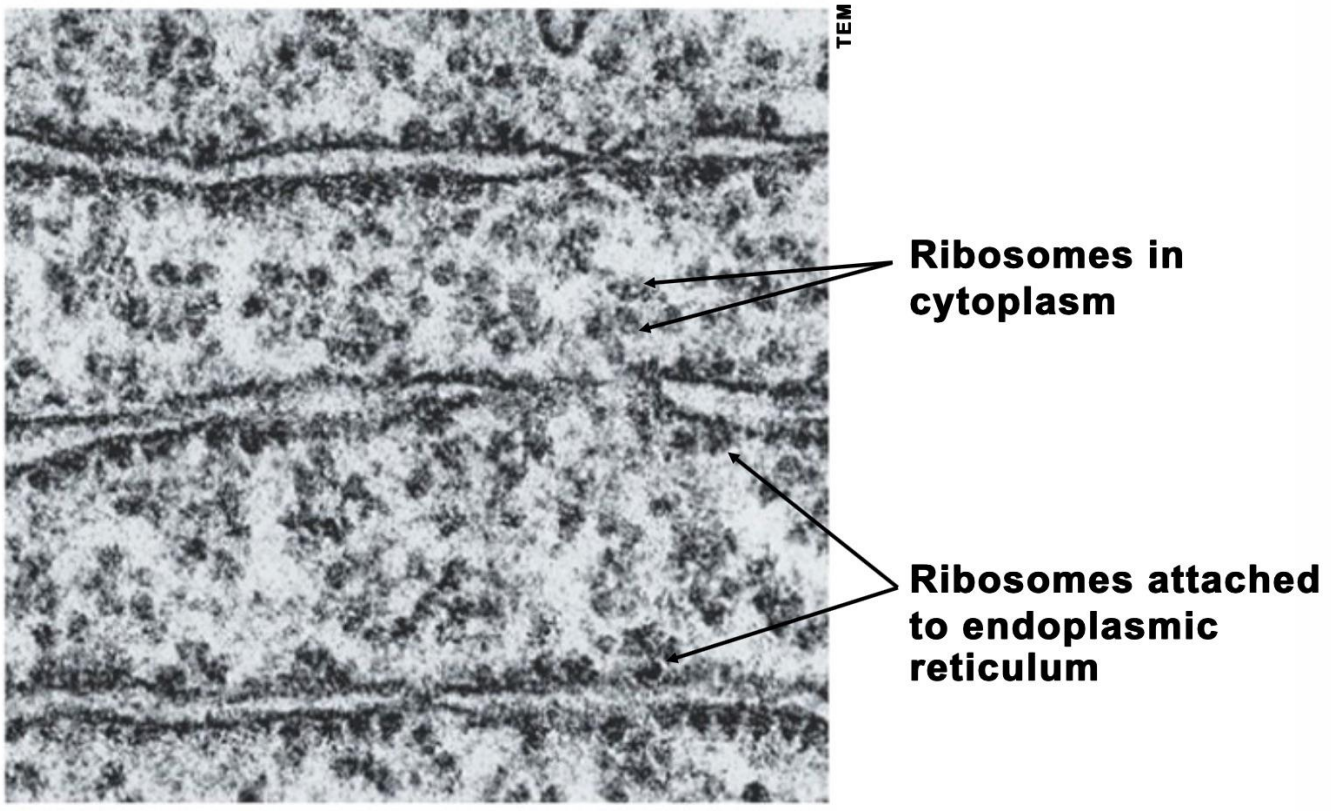
Ribosomes to a Hematologist or Geneticist



Ribosomes to a Cell Biologist

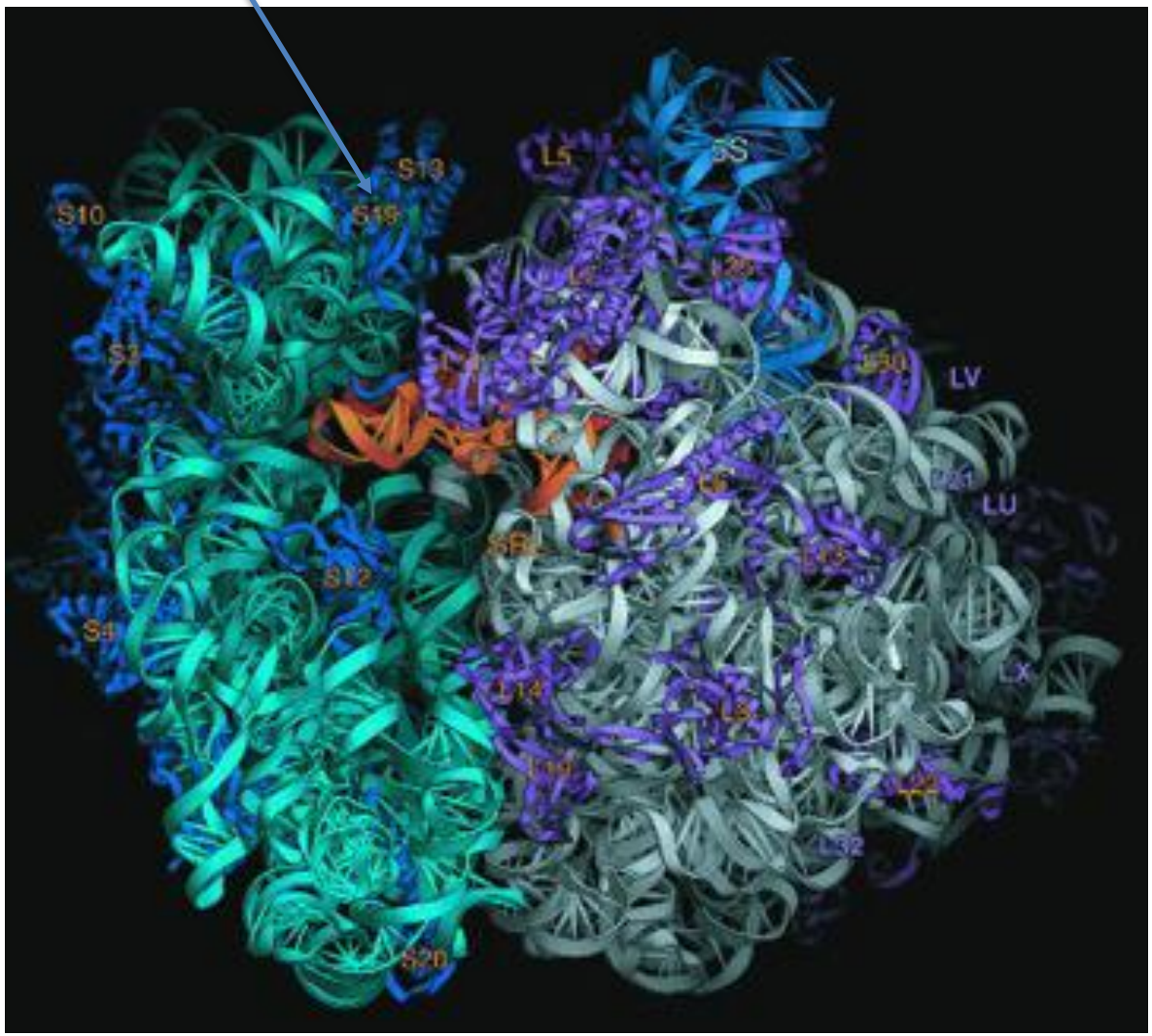


The anemia in DBA results from the inability of GATA1 mRNA to effectively compete for translation when there are suboptimal levels of ribosomes, which in turn affects RBC development

Are there polymorphisms in the human population where the clinical features of associated with these polymorphisms are only observed when you have suboptimal numbers of ribosomes?

Genetic backgrounds effects will only be discovered through whole exome or whole genome sequencing

Ribosomes to a Ribosome Guy

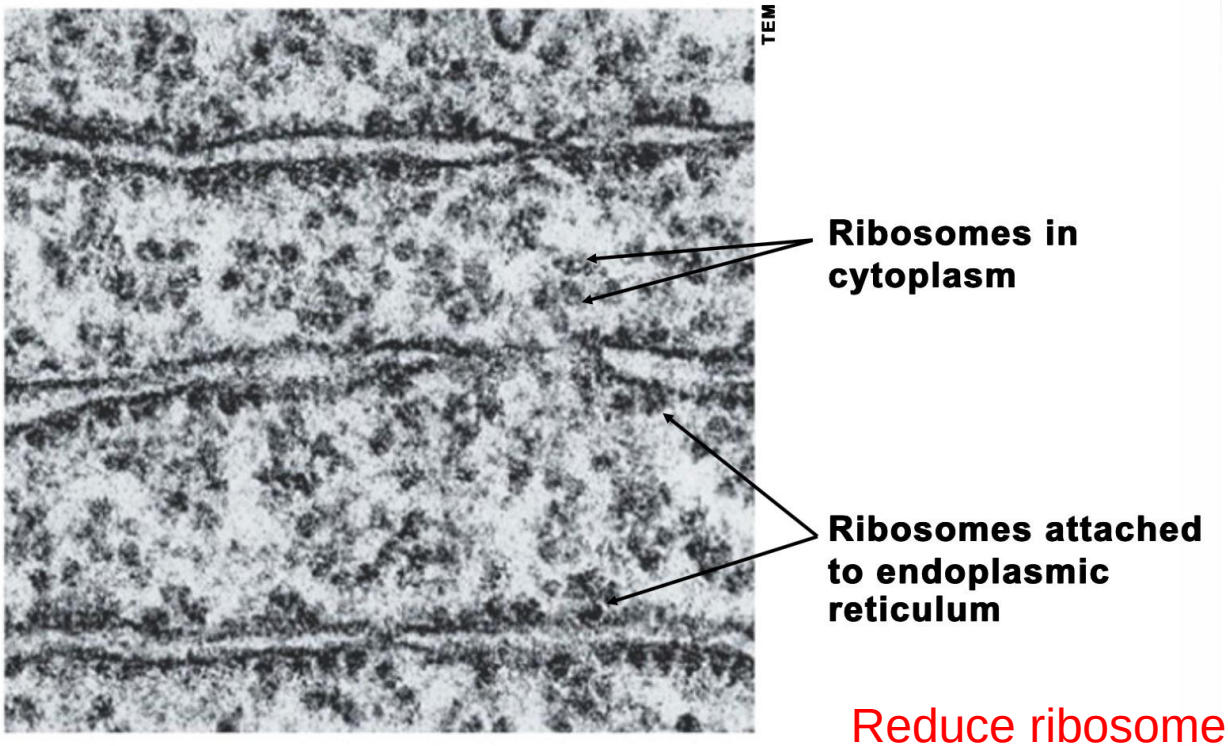


- Large, Structurally complex
  - 80 proteins
  - 4 RNAs
- The fundamental unit of life
- Every living organism on the planet, from garden variety bacteria, to bacteria living in thermal vents in the ocean to humans, have similar ribosomes
- The ribosome is an RNA machine, with ribosomal proteins added later to facilitate assembly and make improvements on function

Your Foundations at Work (Variability in Clinical Phenotype)

12/2018 The DBAF has awarded $54,754 with support of $5,000 from DBAC and $10,000 from Friends of DBA to Dr. Scott C. Blanchard, PhD, from Weill Cornell Medicine for the project entitled “Identifying associations between DBA and genomic variation in ribosomal DNA”.

The Number of Ribosomes per Cell Correlates with Growth Rate



- Speed up cell division, increase ribosome number
- Slow down cell division, reduce cellular number

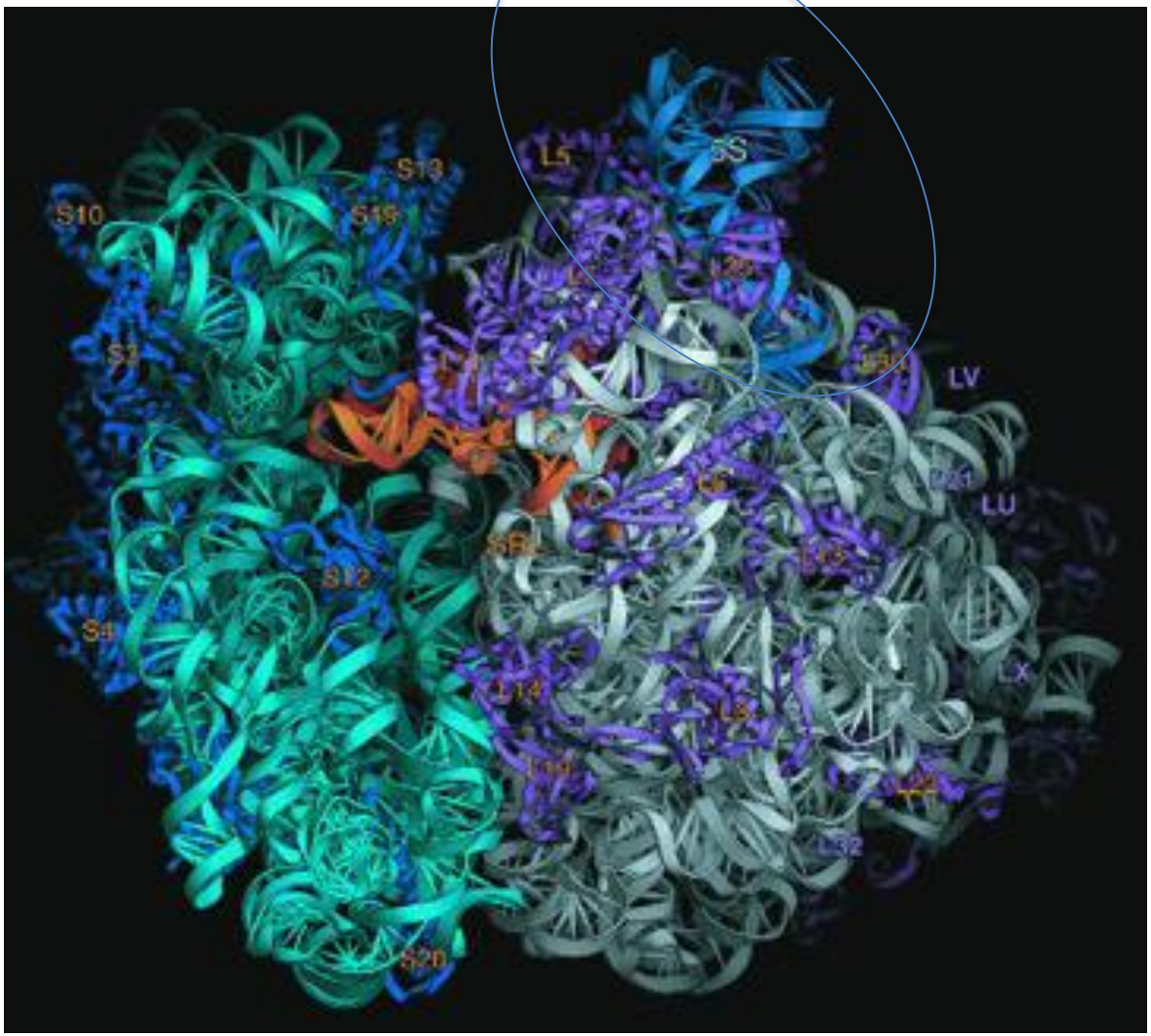
Reduce ribosome number, reduce growth rate

Genes that speed up cell division and increase the number of ribosomes per cell are oncogenes – c-Myc

Genes that slow down cell division and decrease the number of ribosomes per cell are tumor suppressor genes – p53

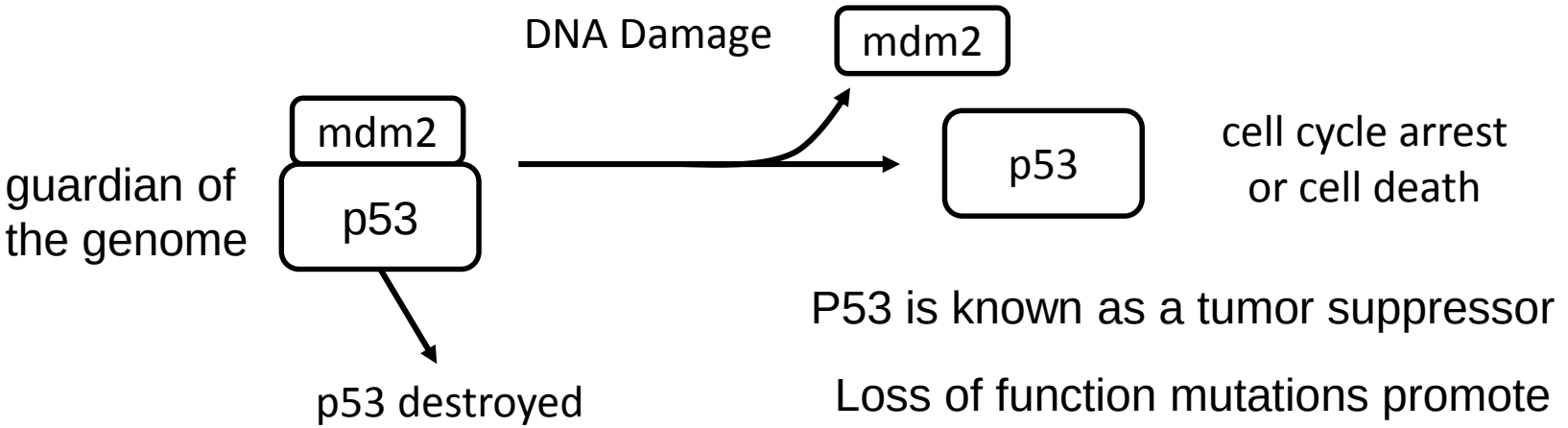
Focus on the 5S RNP (Rpl5, Rpl11, 5SRNA)

5S RNP: Rpl5/11



- 5S RNP forms a subcomplex prior to being incorporated into the large subunit and can exist as an independent entity apart from the ribosome
- We now know that this complex plays a critical role signaling ribosomal stress to factors involved in regulating cell growth and ultimately life or death decisions at the cellular level.

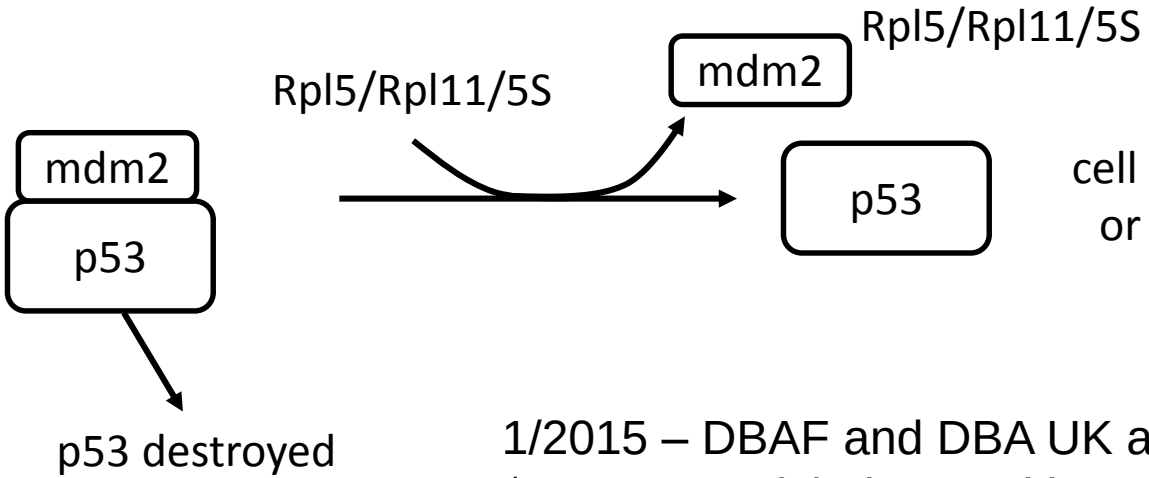
Ribosomal Stress Model for DBA Pathophysiology



P53 is known as a tumor suppressor

Loss of function mutations promote cancer progression

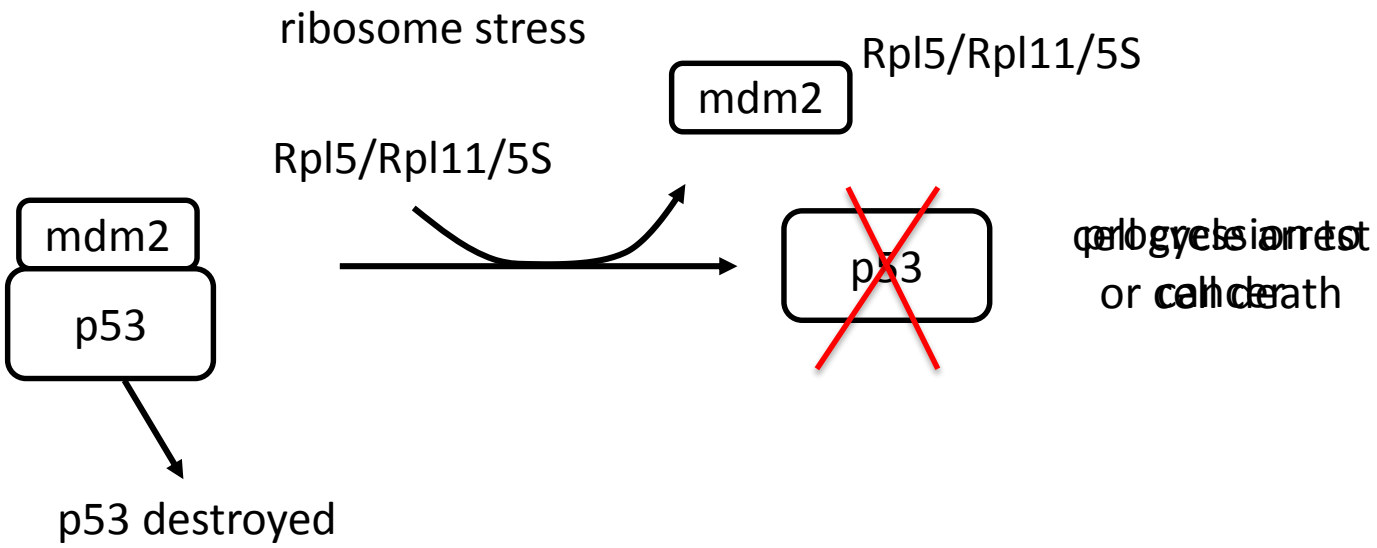
ribosome stress (autosomal dominant RP mutation)



1/2015 – DBAF and DBA UK awarded a grant of $41,810 to Nicholas Watkins to study the role of RPL5 and RPL11 in signaling p53 activation

Keersmaecker's Reformulation of Dameshek's Riddle

How does a disease with a hypoproliferative phenotype transition to cancer and a hyperproliferative phenotype?



Your Foundations at Work (Cancer Predisposition)

The DBAF awarded a grant for $50,000 to Dr. Lionel Blanc, PhD, who is at the Feinstein Institute for Medical Research in New York City, with co-investigator Dr. Jeffrey Lipton. The project is entitled, “Beyond the erythron, skeletal defects in Diamond Blackfan anemia.” The overall goals of this research are (1) to understand the defects in bone development (poor linear growth, osteopenia, skeletal anomalies) as a consequence of RP haploinsufficiency (2) to acquire a fuller understanding of the etiology of osteogenic sarcoma in the context of DBA, and thus (3) to determine the role of ribosomal protein gene mutations in oncogenesis, using DBA as a model.

Your Foundations at Work (New Drug Development)

4/2015 – DBAF and DBAC awarded a grant of $35,000 to Johan Flygare to help start up a new lab and screen a library of over 12,000 chemical compounds to identify potential drugs that alleviate the symptoms of their mouse model of DBA

EuroDBA 2019 - Dr. Flygare reported that this screen turned up a series of compounds all of which act through the inhibition of a protein kinase known as CDK8

- Rescues the DBA phenotype in RPS19 mice
- Rescues the DBA phenotype in $CD34^+$ cells from DBA patients with three distinct genotypes

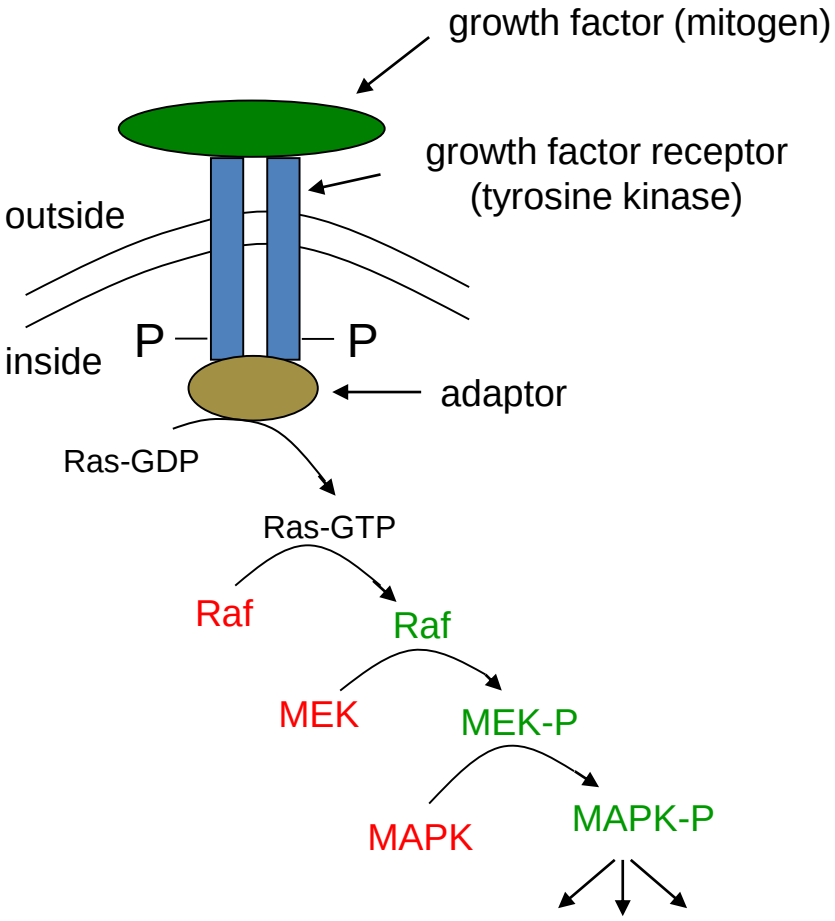
Mechanism of action

- Reduces the expression of p53 target genes in response to ribosomal stress
- Increases the expression of C-myc regulated genes including several ribosomal proteins

Your Foundations at Work (New Drug Development)

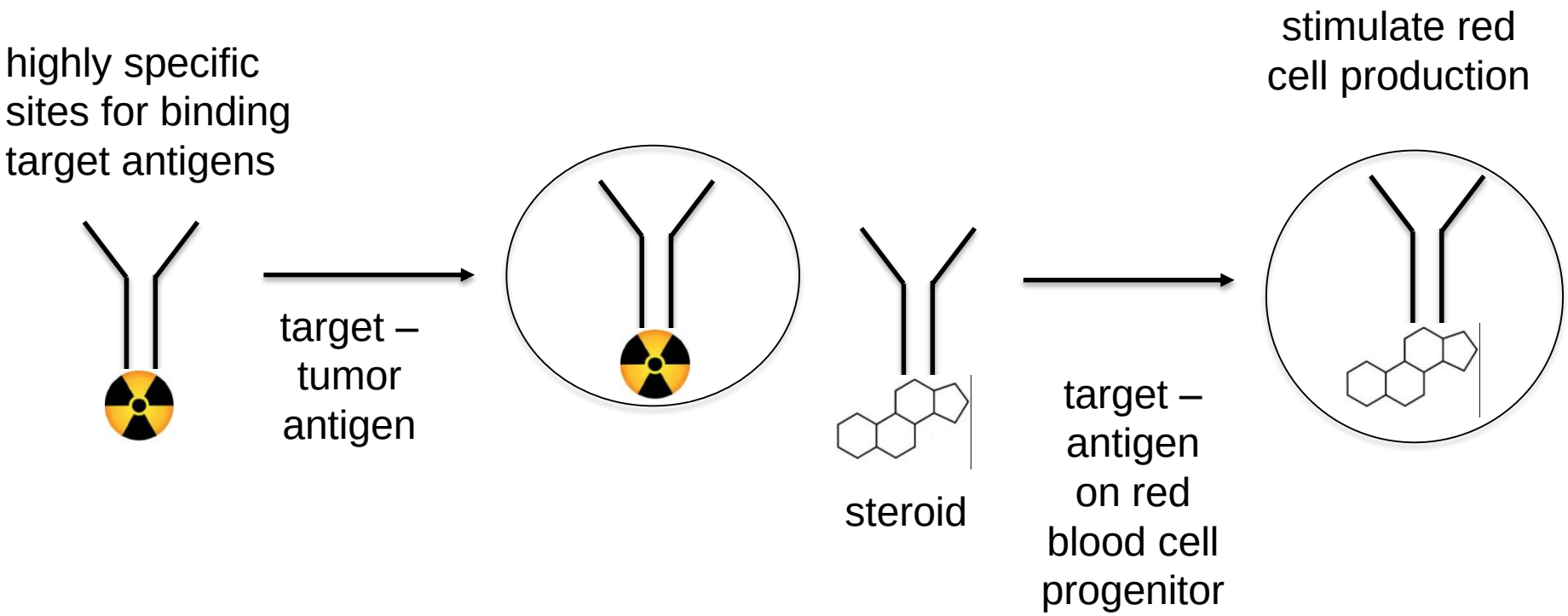
3/2019 The DBAF awarded a grant to Dr. Kathleen Sakamoto, a professor in the School of Medicine at Stanford University, for $62,409 with support of $10,000 from DBA Canada and $20,000 from Friends of DBA. The project is entitled "Targeting Nemo-like Kinase for the Treatment of Diamond Blackfan Anemia."

Do the kinases identified by Flygare and Sakamoto converge on a common mechanism?



Your Foundations at Work (Newer Drug Development)

2/2018 The DBAF has funded $75,000 with support of $20,000 from DBA Canada and $10,000 from Friends of DBA to Johan Flygare, M.D., Ph.D. at Lund University in Sweden for his project entitled, “Targeted corticosteroid therapy for DBA.”



Your Foundations at Work (Gene Discovery)

7/2017 A DBAF grant of $56,021 was awarded to Vijay G. Sankaran, M.D., Ph.D., Harvard Medical School, Broad Institute of MIT and Harvard, Boston Children's Hospital, Boston, MA for the project, "Dissecting the genetic architecture of Diamond Blackfan anemia." The goal of this proposal is to mine whole exome sequencing data to identify novel genes responsible for DBA.

The Genetic Landscape of Diamond-Blackfan Anemia 2018 Am. J. Hum. Genet.

445 affected individuals subjected to whole exome sequencing, ~ 70% had identifiable mutations, most in known genes but also some possible new genes

11/2017 A DBAF grant of $20,000 was awarded to Dr. Anna Aspesi, a junior investigator who for the past 14 years has been working in various capacities (graduate student, postdoctoral fellow) in the laboratory of Dr. Irma Dianzani at the Universita del Piemonte Orientale in Novara Italy for the project entitled, "The problem of interpreting missense mutations of DBA genes: proposal of a new functional assay. "

Direction of DBA Research (2017 Predictions)

Breakthrough in one of the drugs currently or soon to be tested

Physicians like Drs. Vlachos and Lipton will still have their hands full with clinical trials

New drugs will continue to flow down the research pipeline

Much better handle of the mechanisms behind and the management of complications of DBA

Direction of DBA Research (2019 Predictions)

Better and Brighter Future