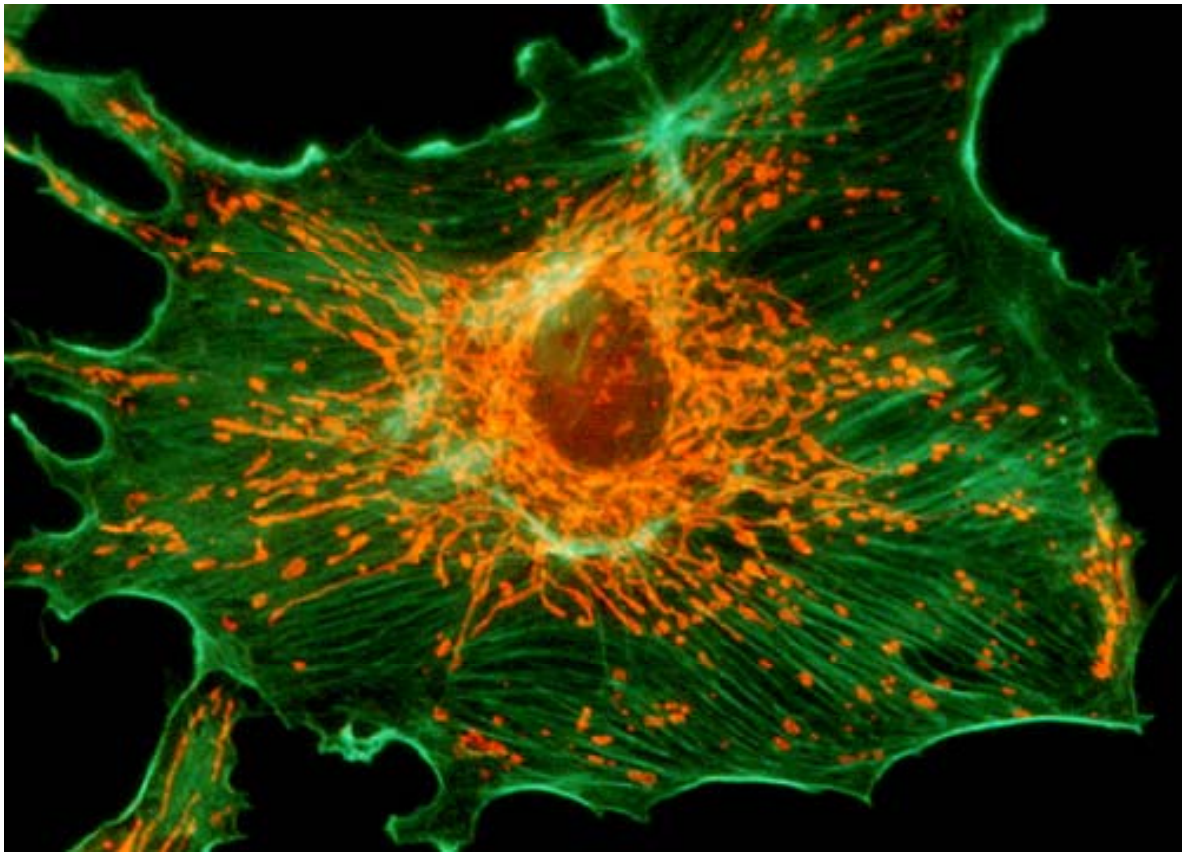
mitochondria genome instability & cancer progression

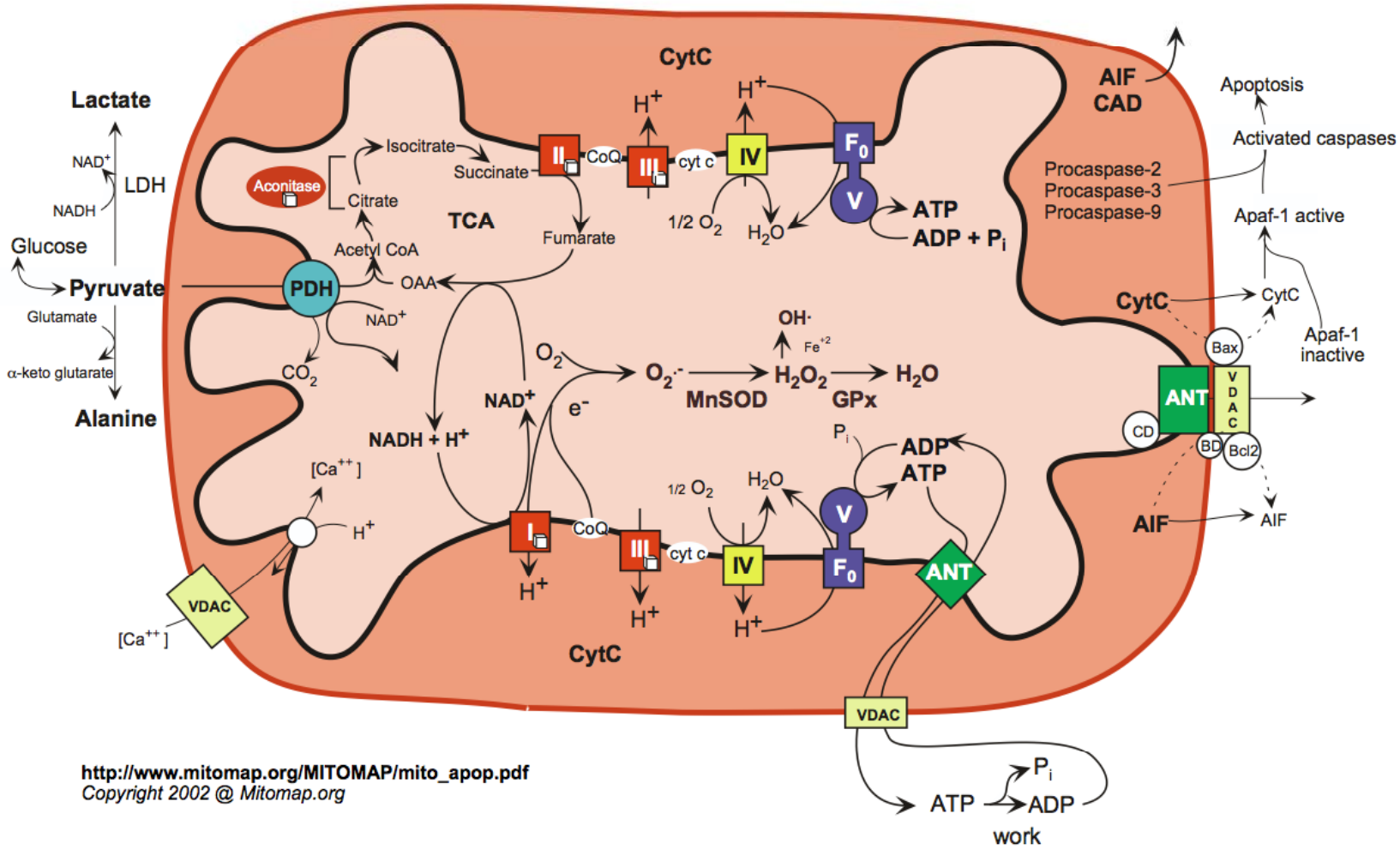


Robin Coope, Lindsay De Vorkin, Spencer Martin, Jill Mwenifumbo, Joanna Wegrzyn & Denil Wickrama

Bovine Pulmonary Artery Cell Mitochondria and Actin. http://www.microscopyu.com/articles/fluorescence/filtercubes/dual/fitctritc/fitctritcbpae1large.html

background

mitochondrial function



background

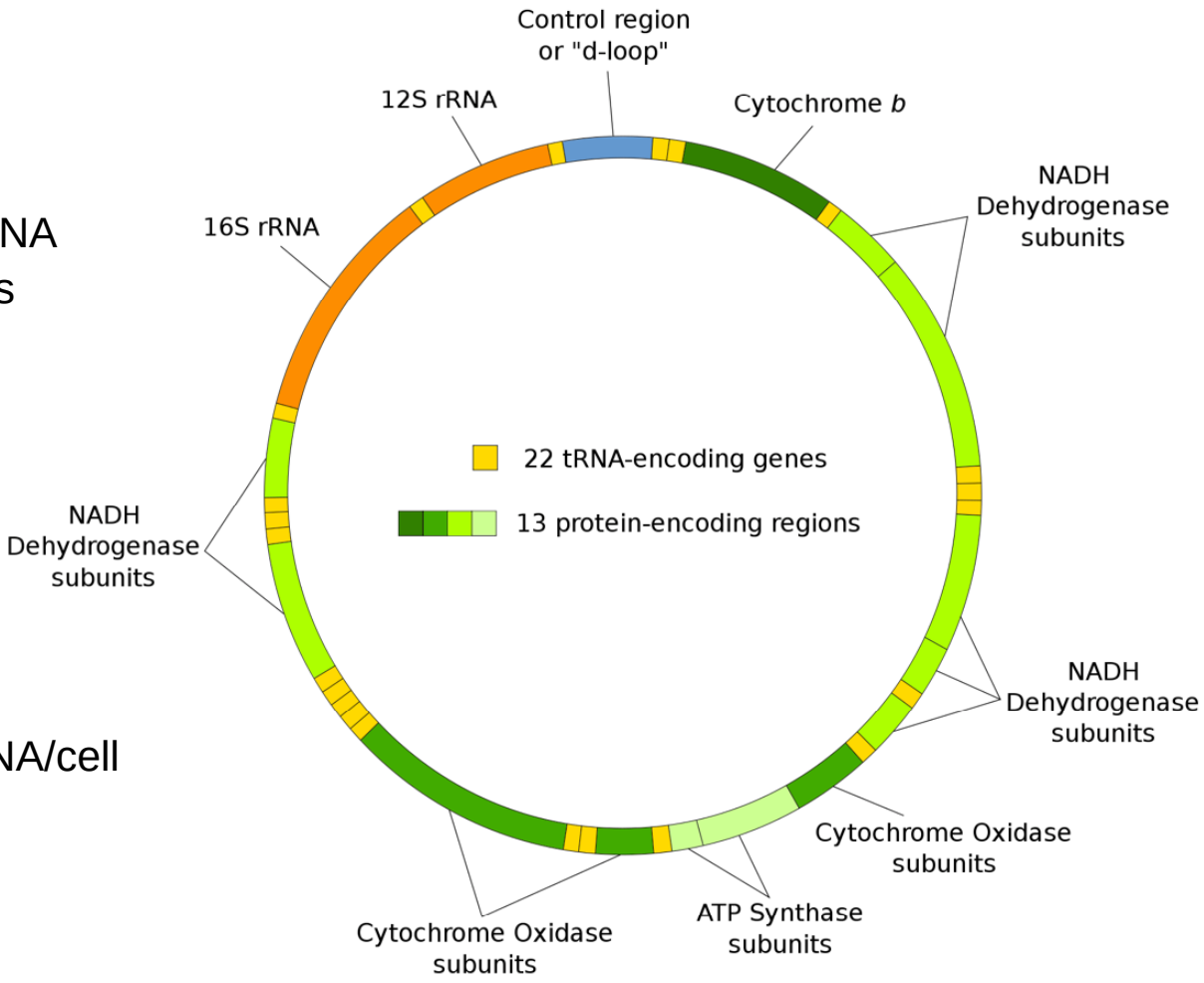
mitochondrial DNA

double-stranded circular mtDNA molecule is 15 569 base pairs

37 genes

- 13 are for proteins
- 22 are for transfer RNA
- 2 ribosomal RNA

100 to 10 000 copies of mtDNA/cell



Wikimedia Commons http://en.wikipedia.org/wiki/File:Mitochondrial_DNA_and_diseases.png

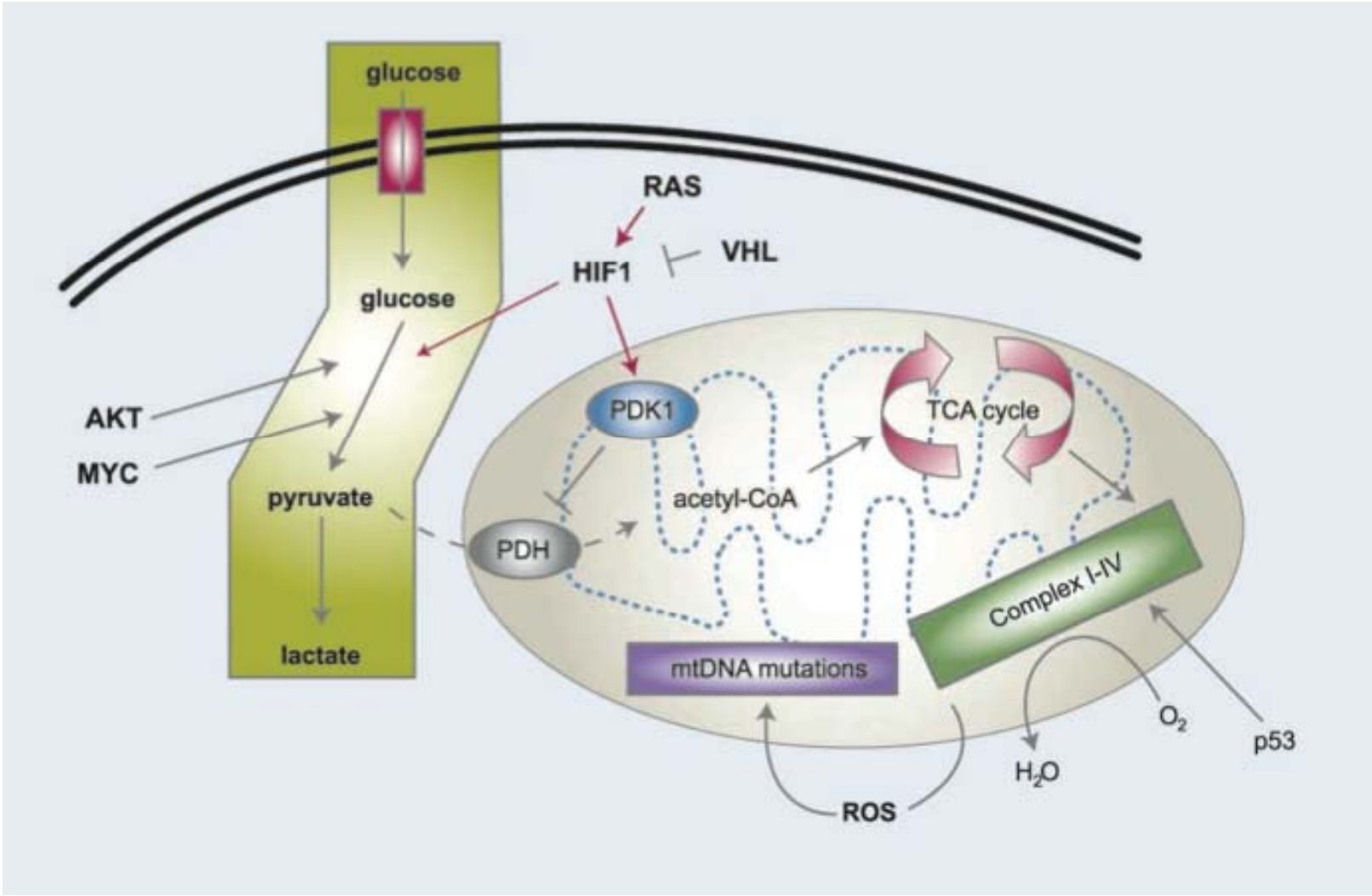
background

somatic mitochondrial mutations in cancer

Chatterjee A, Mambo E and Sidransky D (2006). Mitochondrial DNA mutations in human cancer. Oncogene, 25, 4663-4674

background

the Warburg effect: mitochondria & cancer



Vander Heiden MG, Cantley LC, Thompson CB (2009) Understanding the Warburg Effect: The Metabolic Requirements of Cell Proliferation.Science, 324(5930);1029-1033

background

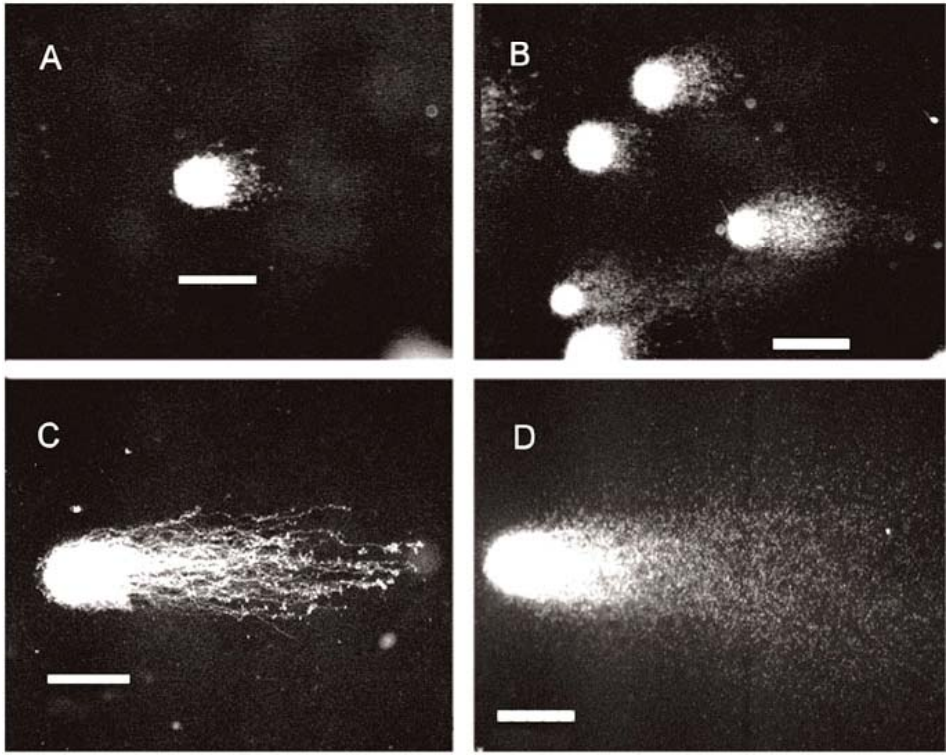
reactive oxygen species & dna damage

DNA is a major target of oxidative damage

8-oxoguanine is one of the most common forms of oxidative DNA damage

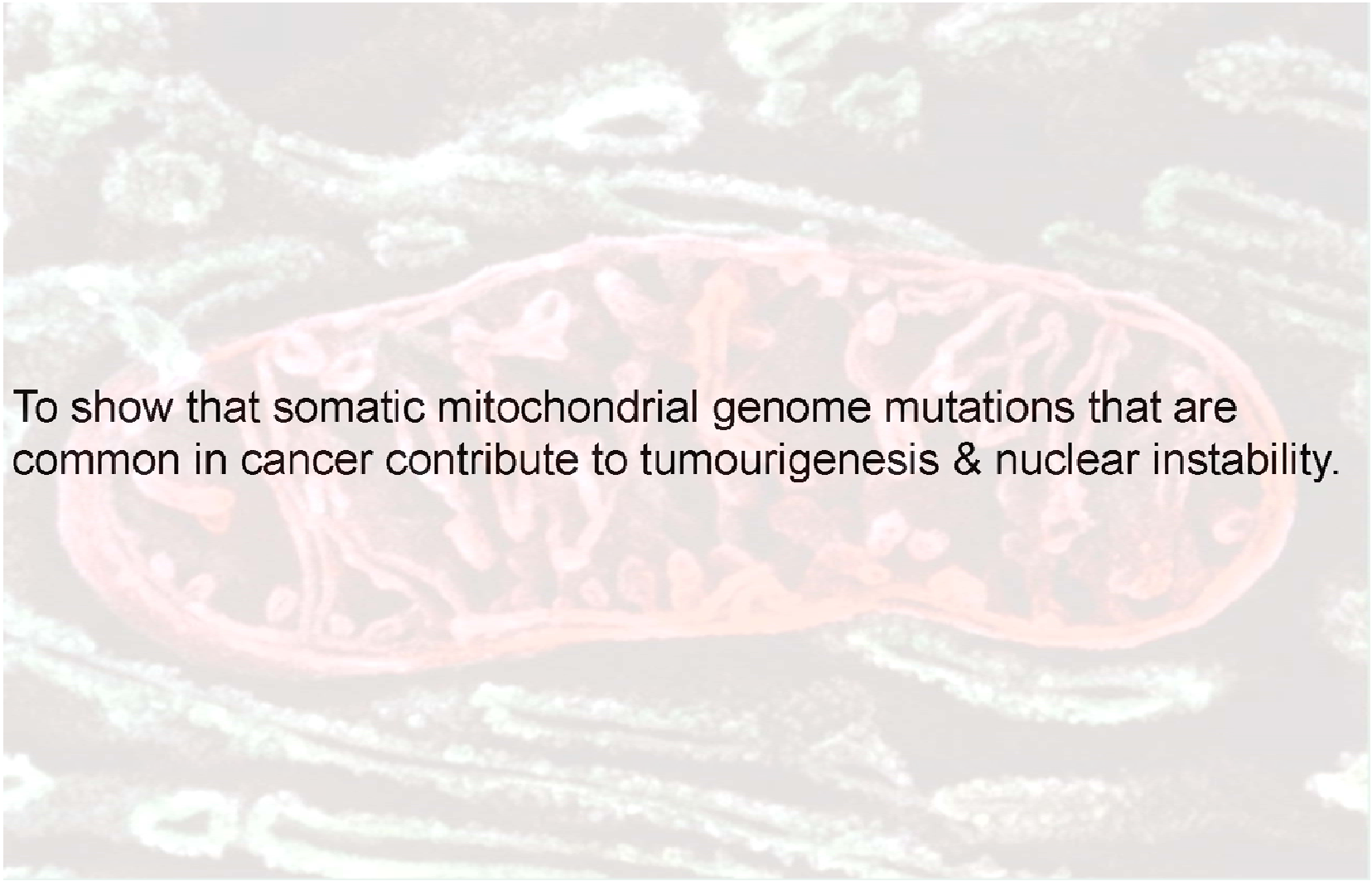
introduces non-native chemical bonds or bulky adducts

failure to repair this lesion leads transversion mutations



We propose that somatic mtDNA mutations and the resultant respiratory dysfunction may be linked directly to tumorigenesis via reactive oxygen species and genomic instability.

objective



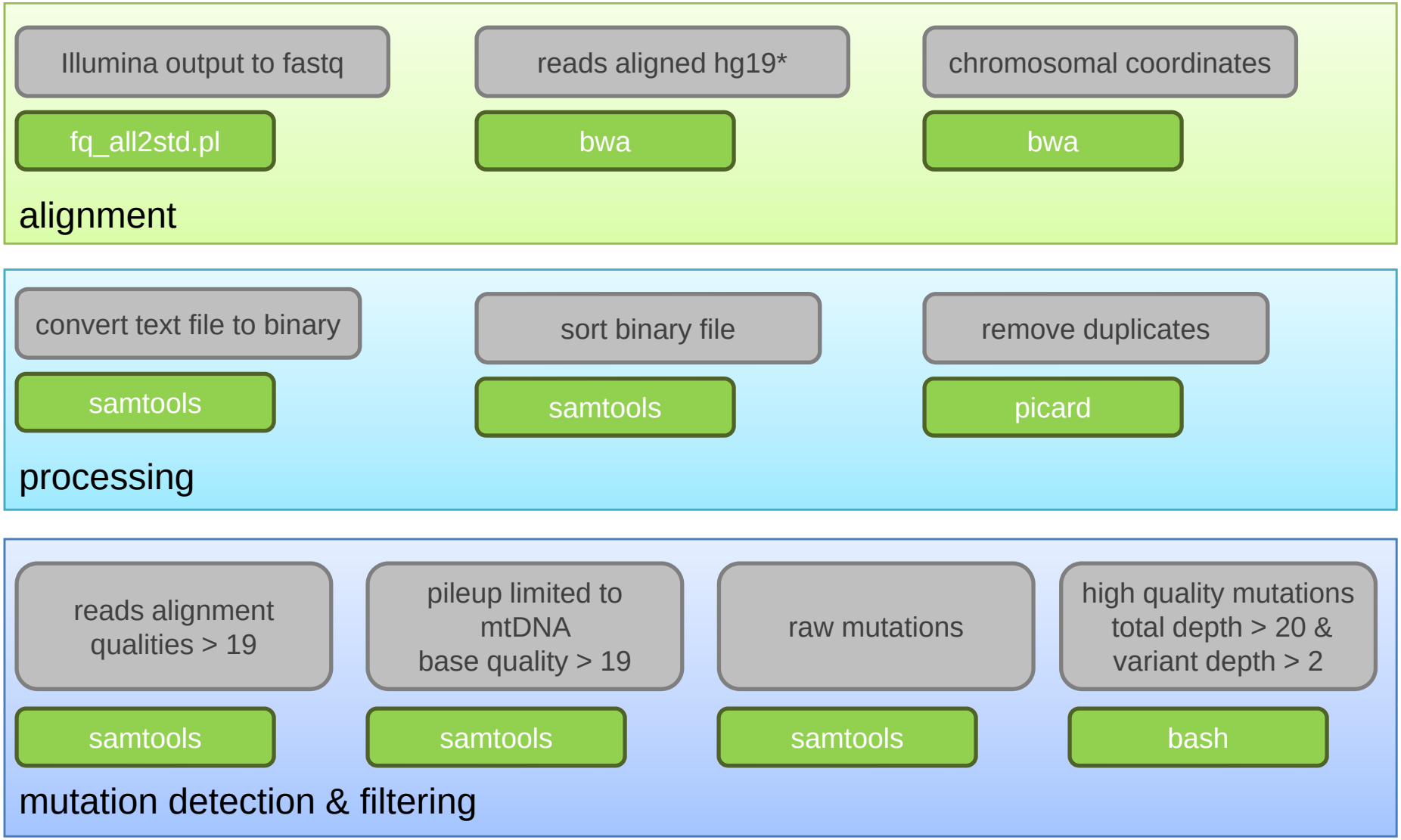
Scanning electron micrograph of a mitochondrion in an intestinal epithelial cell. P. Motta & T. Naguro/Photo Researchers, Inc.

aims

BIOINFORMATICS	somatic mutation in the mtDNA
FUNCTIONAL CHARACTERIZATION	tumor progression
BIOCHEMISTRY	ROS & DNA adducts
MOLECULAR BIOLOGY & BIOINFORMATICS	genomic instability

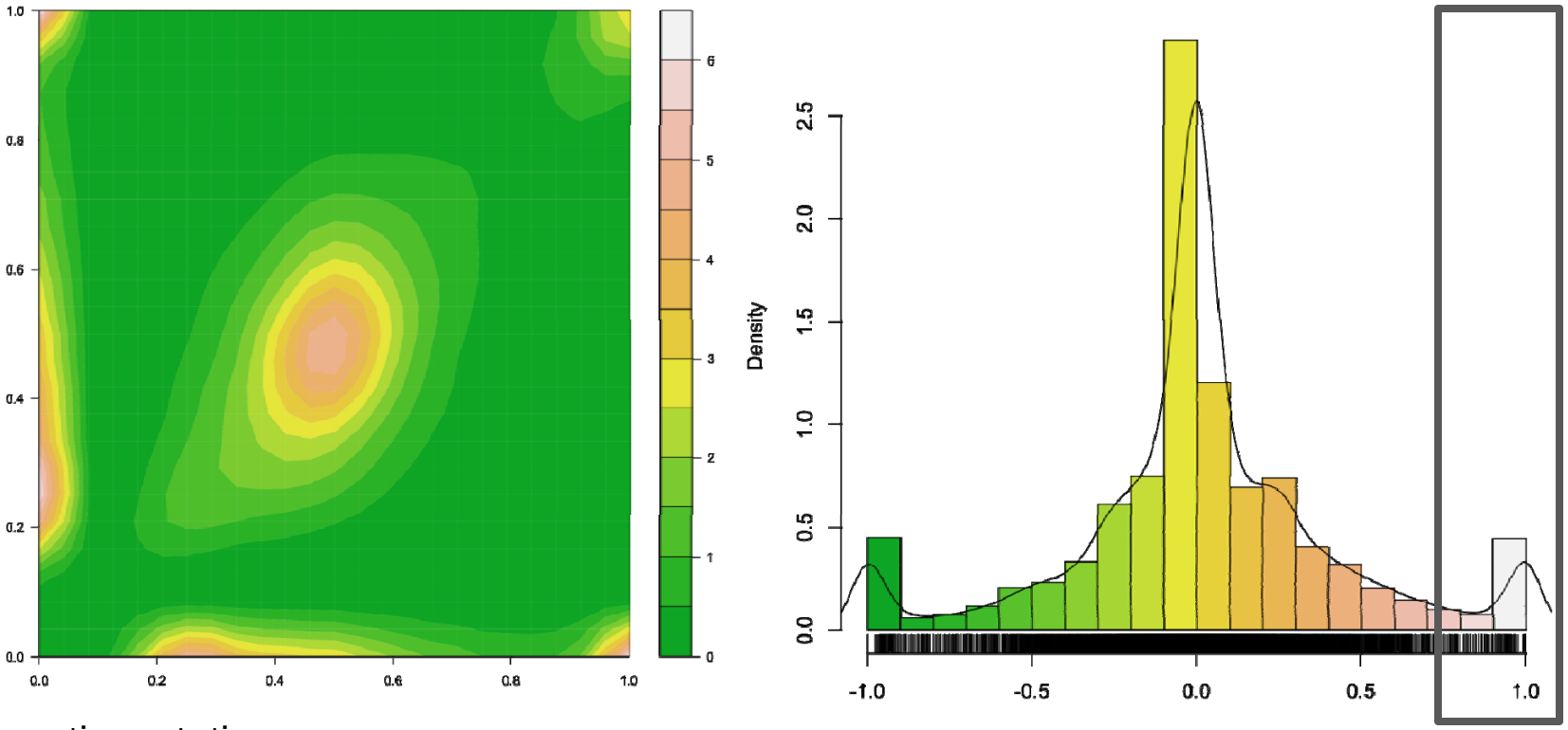
techniques & methods

bioinformatics analyses



techniques & methods

bioinformatics analyses



somatic mutations

recurrent somatic mutations

techniques & methods

clinical collaboration & tissue collection

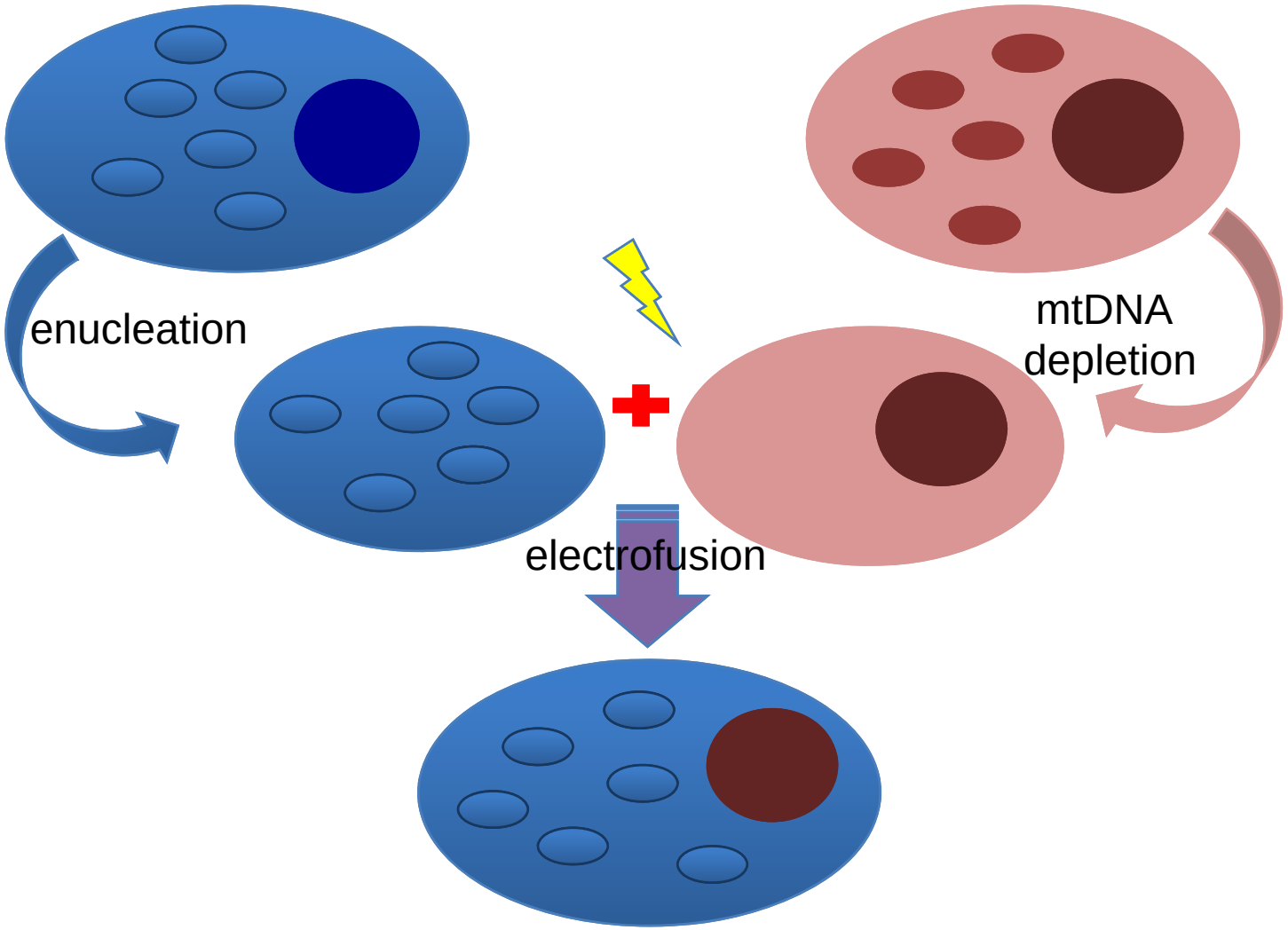
BCCA tumor tissue repository in Victoria, BC

protocol to save viable cells from patient samples

derive cell lines from tumour and matched normal samples

techniques & methods

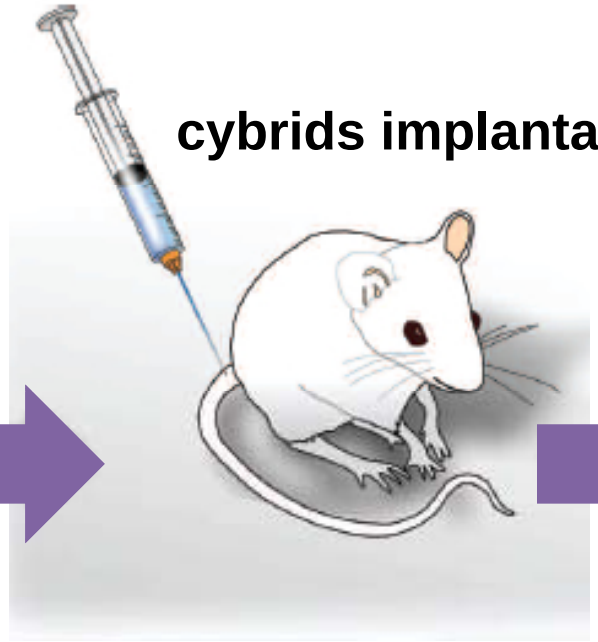
transmitochondrial cybrid generation



techniques & methods

xenotransplant

transmitochondrial cybrids production



tumor growth assessment

analysis

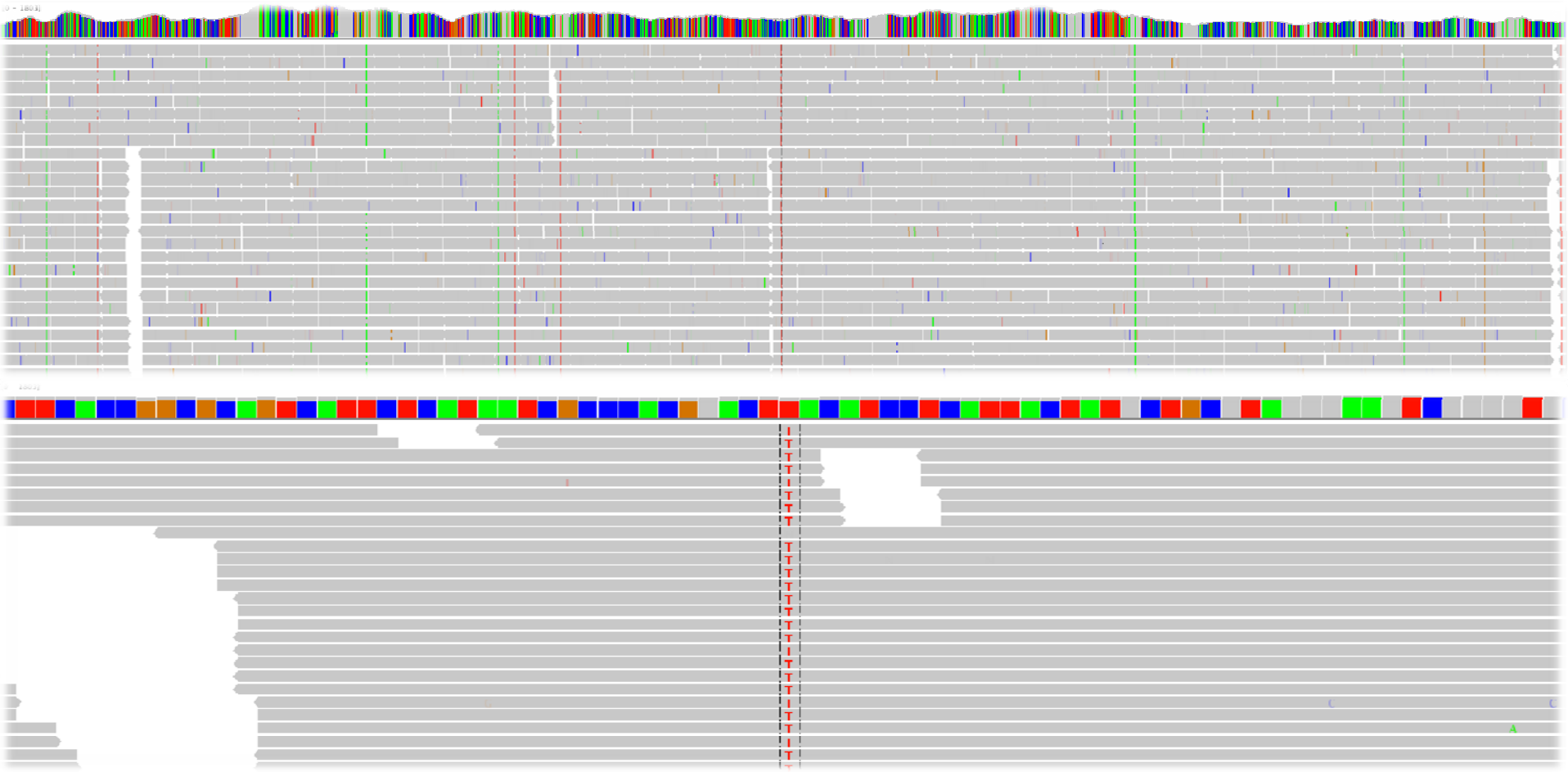
tumor assessment
growth
time to euthanasia
TNM stage

tumor DNA damage assessment
reactive oxygen species
DNA adducts
global nuclear genomic DNA integrity

tumor nuclear genomic DNA stability
karyotype
microsatellite
next-generations sequencing

problems & solutions

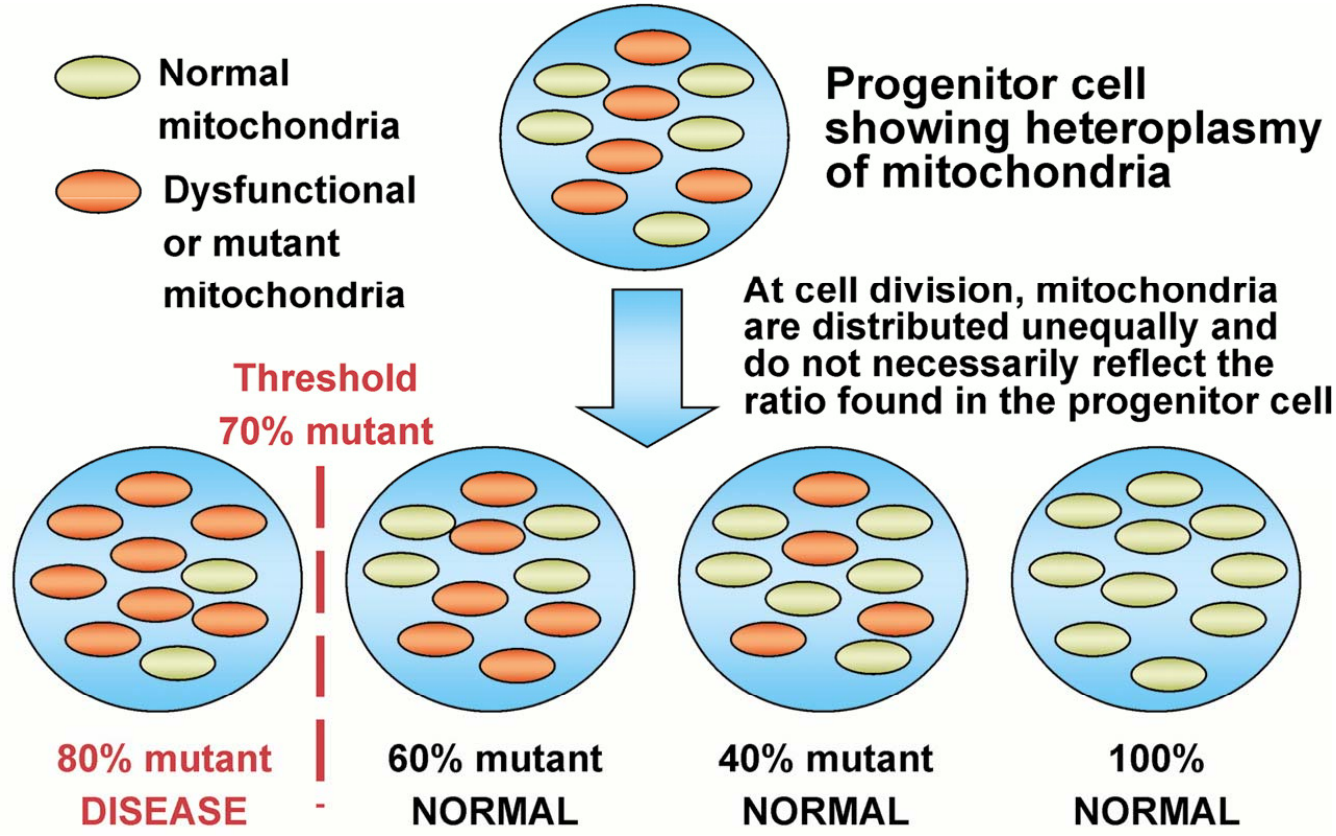
P1: heterplasmy, tumor heterogeneity & stromal contamination



S1: Any mutation that changes in frequency (≥70%) from the matched normal to the cancerous tissue will be defined as somatic mutations of interest (SNVs).

problems & solutions

P2: threshold of pathogenecity



S2: Any mutation that changes in frequency (≥70%) from the matched normal to the cancerous tissue will be defined as somatic mutations of interest (SNVs).

White, AJ (2001). Mitochondrial toxicity and HIV therapy. Sex Transm Infect, 77:158-173.

significance

Mitochondrial defects have long been suspected to play an important role cancer, however critical analysis of the role of mitochondrial dysfunction in genome instability and tumor progression is lacking.

To our knowledge, this study will be the first to analyze next-generation mitochondrial sequence data to identify mtDNA mutations that enhance nuclear genome instability and promote tumourigenesis.

By combining sequencing data with functional characterization of somatic mtDNA mutations, our study will be an important and novel contribution to cancer research.

Altman's Army

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