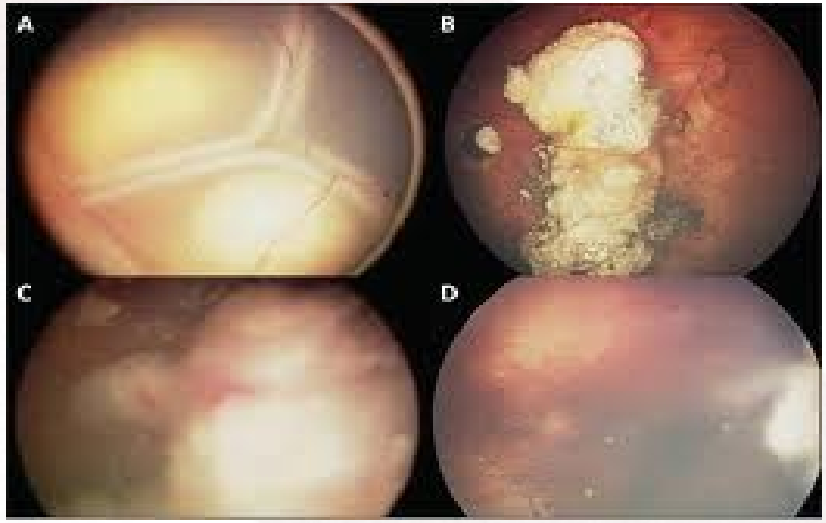
Retinoblastoma:
the Dangerous White Eye



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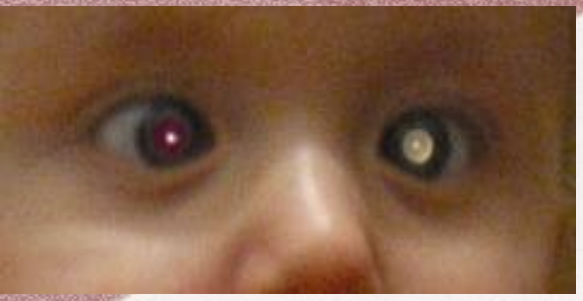
Physiology

Fig 1



- Incidence Rate: 1 in 18,000 and 30,000; No Racial Bias
- Incomplete penetrance – may inherit but not express mutation
- Can be bilateral (affecting both eyes) or unilateral (affecting only one eye): Unilateral are frequently due to spontaneous mutations, while bilateral are due to germline mutation

SYMPTOMS

• Leukocoria: a “white eye” shows rather than typical red eye when light is shone into the eye; this is due to the eye neoplasm – a tumor

•Strbismus: squinting

• Lazy Eye: A rare sign – as lazy eye can occur in other cases

• Conjunctivitus

•Visual Disorientation

•Dymorphic features – occurs if there's a deletion of 13q; includes bulbous tip nose, large mouth, thin upper lip, protruding upper incisors, if serious: may have finger and/or toes abnormalities, and mental retardation

- Many patients have little or no visibility of abnormality

• Early Onset:

- Bilateral cases are shown in the first year
- Unilateral cases are shown between 24 to 30 months

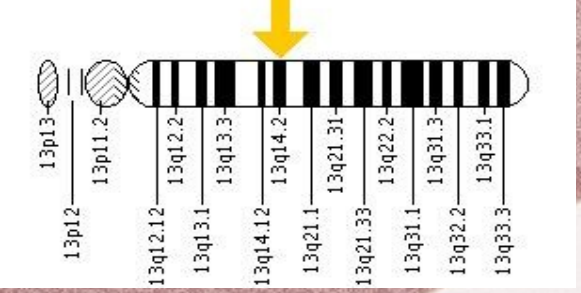


Fig 3

Molecular Cause

- Mutation in tumor suppressor gene that codes for Rb protein, located at 13q14.1 and 14.2
  - Over 900 reported cases of mutation (~ 930)
- Autosomal Dominant
- Can be spontaneous or germline mutation; most germline mutations are from paternal allele, and equal frequency from either allele in somatic
- Caused by mutations or deletion.
  - Mutations within coding regions destabalizes Rb or compromises its association with enzymes
  - Mutation within the promoter region causes reduced expression of Rb
  - Either way results in loss of functional RB
  - One hotspot for mutation is the C to T transition in CGA codons at exons 8, 10,11 14, 15, 17, 18, 23
- Loss of Heterozygosity: receiving one mutated copy and one normal, but normal becomes mutated
  - *Two Hit Hypothesis* – Second hit is the mutation of the normal copy; may be due to interstitial deletion, mitotic recombination or nondisjunction
- Gene can be silenced by hypermethylation of CpG Islands in promoter region, and Rb protein cannot be created at all

Molecular Pathway

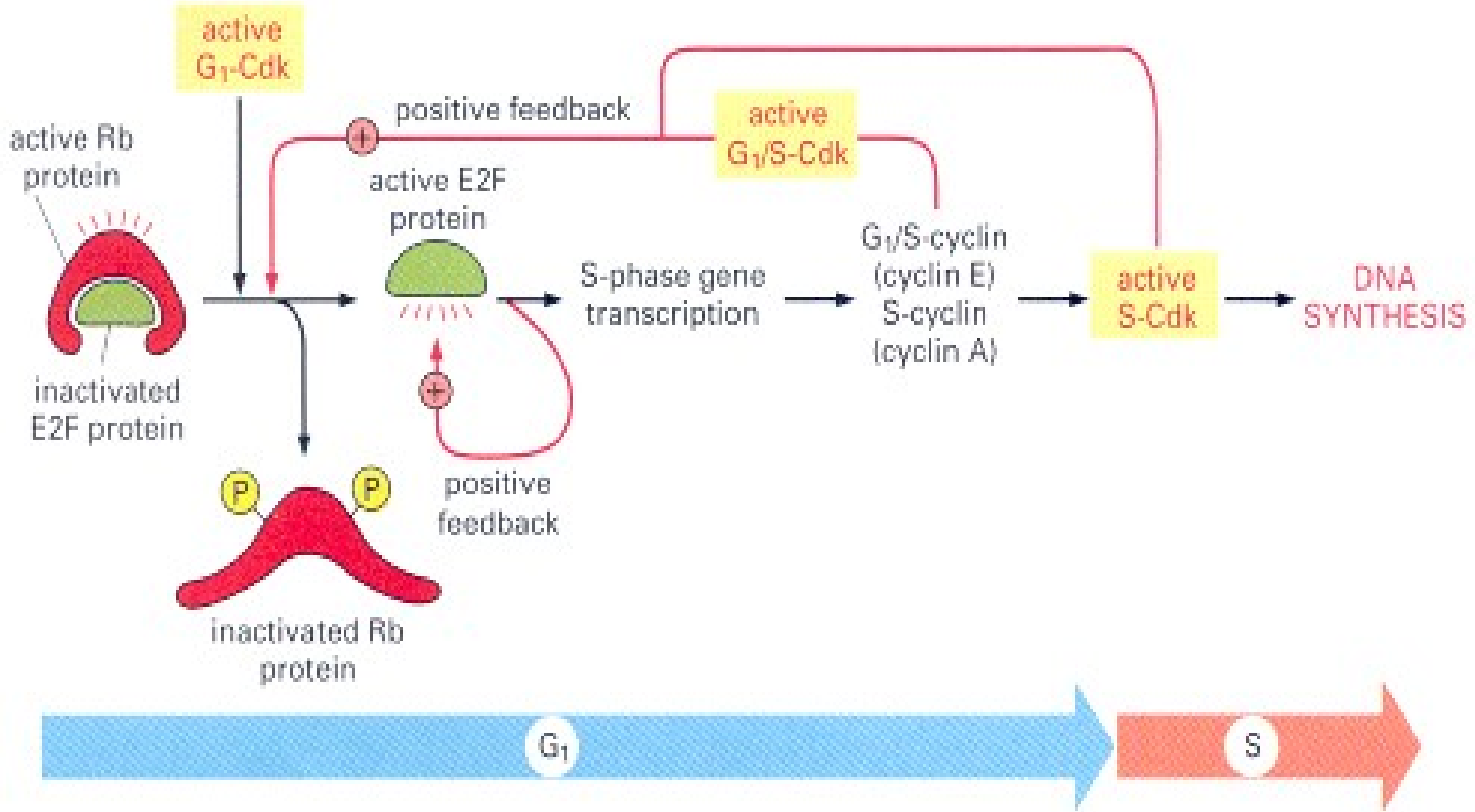


Fig 2

Current Treatments

Treatments undergoing clinical studies:

- Ophthalmic arterial infusion therapy
  - Tube sent through ophthalmic artery to send anticancer drugs
- High-dose chemotherapy with stem cell treatments
- Biologic therapy
  - Immune system is given a boost to fight tumor cells

Problems to kept in mind:

- Preservation of sight; scarring
- Damage to adjacent healthy tissue
- Tumor recurrence
  - In unilateral, neoplasm may occur in other eye

Diagnosis:

- Symptoms and medical imaging
- If yes, the child would be referred to a specialized doctor who would examine an image of the eye under microscope

- Chemotherapy
  - Systemic chemotherapy
  - intra-arterial
- Thermotherapy
- Radiation Therapy
  - External Beam Radiation Therapy (EBRT)
  - Intensity Modulated Radiation Therapy (IMRT)
  - Brachytherapy
  - Proton-Beam Radiation
  - Stereotactic Radiation
- Brachytherapy
- Cryotherapy
- Photocoagulation
- If all fails, Surgery.

Proposal & Limits

- Targeting CpG islands hypermethylation
  - Use restriction Type II restriction enzymes to cut out the promoter.
  - Send the enzyme, and a normally hypermethylated promoter via adeno-associated viral vectors through optimal artery
    - Adeno-associated viral vectors can be programmed to integrate its cargo at a specific chromosome, so these vectors will target chromosome 13; vectors will also need to have special protein receptors for retinal cells on its membrane.
- Instead of using the same method for mutations, I will use the SmaRT (Spliceosome-Mediated RNA Trans-splicing) process instead. This method repairs mRNA by replacing the spliced regions with a normal region.
  - An RNA strand that pairs with the intron next to the mutated segment is sent to prevent splicosomes from incorporating the mutated portion. As the same time, the correct mRNA is delivered through liposomes and put in place of the mutated mRNA
- Since retinoblastoma has an incredibly early onset, dealing with mutations pre-natally would be best:
  - Take out embryo, and inject cationic lipids with restriction enzyme and with corrected gene.
- One final treatment would be injection of Rb protein directed at eye in liposomes via the optimal artery – this would be a life-long plan and should be started at birth, literally.

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Fig 1:http://waltr.net/oncology/html/peds/img/Rb_whiteeye.PNG

Fig 2:
http://dpuadweb.depauw.edu/cfornari_web/DISGEN/retinoblastoma_website/public_html/protein.htm

Fig 3:http://ghr.nlm.nih.gov/gene/RB1

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