BIOC 5001 ***Special Topics in Biochemistry and Molecular Biology:*** **DNA REPAIR**

Coordinator: Dr. Graham Dellaire

12 Week course of directed readings on DNA Repair

(Detailed outline attached)

Week 1-4. (Sept 10-Oct 1, 2010)
Introduction to DNA damage and DNA Repair

Week 5: (Oct 8, 2010)
Diseases Associated with defective nucleotide excision repair (NER)

Week 6-7: (Oct 15-22, 2010)
Diseases Associated with genomic instability and DNA strand breaks and defective double stranded break (DSB) repair

Week 8: (Oct 29, 2010)
Diseases Associated with defects in non-homologous end joining (NHEJ)

Week 9: (Nov 5, 2010)
Diseases Associated with defective mismatch repair (MMR)

Week 10: (Nov 19, 2010)
Diseases Associated with cell cycle response to DNA damage

Week 11: (Nov 26, 2010)
Diseases Associated with defective DNA helicase function and involved in aging

Week 12: (Dec 3, 2010)
Genome instability and its role in cancer development and progression

Grade is based on:
20% Participation in weekly discussions of directed reading (journal club style)
40% Term paper in the style of a journal review article (10 pages double spaced)
40% Seminar style presentation of a topic in DNA repair (45 min)

BIOC 5001 *Special Topics in Biochemistry and Molecular Biology:* DNA REPAIR

Course Details

Week 1: Lecture: Introduction to DNA damage and DNA Repair (1.5 hr)

- Cell cycle and DNA damage checkpoints
- Overview of types of DNA Damage and mechanisms of repair

DNA Repair and Mutagenesis 2nd Ed. Friedberg et al. 2006
Chapter 2 pgs 9-57

- Single Stranded Break Repair

Dianov GL, Parsons JL.
Co-ordination of DNA single strand break repair.
DNA Repair (Amst). 2007 Apr 1;6(4):454-60. Epub 2006 Nov 22. Review.
Sancar A, Lindsey-Boltz LA, Unsal-Kaçmaz K, Linn S.
Molecular mechanisms of mammalian DNA repair and the DNA damage checkpoints. Annu. Rev. Biochem. 2004 73:39–85)

Week 2: Introduction to DNA Repair

- Base Excision Repair

DNA Repair and Mutagenesis 2nd Ed. Friedberg et al. 2006
Chapter 6 pgs 169-214

- Nucleotide Excision Repair

Costa RM, Chigancas V, Galhardo Rda S, Carvalho H, Menck CF.
The eukaryotic nucleotide excision repair pathway.
Biochimie. 2003 Nov;85(11):1083-99. Review.

Week 3: Introduction to DNA Repair continued

- Translesion Synthesis

DNA Repair and Mutagenesis 2nd Ed. Friedberg et al. 2006
Chapter 15 pgs 539-549

- Mismatch Repair

Jiricny J.
The multifaceted mismatch-repair system.
Nat Rev Mol Cell Biol. 2006 May;7(5):335-46. Review.

Week 4: Introduction to DNA Repair Continued

- Double stranded Break Repair

Wyman C, Kanaar R.
DNA double-strand break repair: all's well that ends well.
Annu Rev Genet. 2006;40:363-83. Review.

- Homologous recombination

DNA Repair and Mutagenesis 2nd Ed. Friedberg et al. 2006
Chapter 18 pgs 663-696

- Non homologous end joining

DNA Repair and Mutagenesis 2nd Ed. Friedberg et al. 2006
Chapter 13 pgs 711-738

- Cell cycle response to DNA damage

DNA Repair and Mutagenesis 2nd Ed. Friedberg et al. 2006

Chapter 20 and 21 pgs 753-804

Week 5: Diseases Associated with defective NER

- Xeroderma pigmentosum
- Cockayne Syndrome
- Tricothiodystrophy

Cleaver JE, Thompson LH, Richardson AS, States JC.
A summary of mutations in the UV-sensitive disorders: xeroderma pigmentosum, Cockayne syndrome, and trichothiodystrophy.
Hum Mutat. 1999;14(1):9-22. Review.
Vermeulen W, Rademakers S, Jaspers NG, Appeldoorn E, Raams A, Klein B, Kleijer WJ, Hansen LK, Hoeijmakers JH.
A temperature-sensitive disorder in basal transcription and DNA repair in humans.
Nat Genet. 2001 Mar;27(3):299-303.

Week 6: Diseases Associated with genomic instability and DNA strand breaks and defective double stranded break repair

- Ataxia telangiectasia
- Ataxia telangiectasia-like disorder
- Nijmegen Breakage Syndrome

Savitsky K, Bar-Shira A, Gilad S, Rotman G, Ziv Y, Vanagaite L, Tagle DA, Smith S, Uziel T, Sfez S, Ashkenazi M, Pecker I, Frydman M, Harnik R, Patanjali SR, Simmons A, Clines GA, Sartiel A, Gatti RA, Chessa L, Sanal O, Lavin MF, Jaspers NG, Taylor AM, Arlett CF, Miki T, Weissman SM, Lovett M, Collins FS, Shiloh Y.
A single ataxia telangiectasia gene with a product similar to PI-3 kinase.
Science. 1995 Jun 23;268(5218):1749-53.
Taylor AM, Groom A, Byrd PJ.
Ataxia-telangiectasia-like disorder (ATLD)-its clinical presentation and molecular basis.
DNA Repair (Amst). 2004 Aug-Sep;3(8-9):1219-25. Review.
Carney JP, Maser RS, Olivares H, Davis EM, Le Beau M, Yates JR 3rd, Hays L, Morgan WF, Petrini JH.
The hMre11/hRad50 protein complex and Nijmegen breakage syndrome: linkage of double-strand break repair to the cellular DNA damage response.
Cell. 1998 May 1;93(3):477-86.

Week 7: Diseases Associated with genomic instability and DNA strand breaks and defective double stranded break repair

- Fanconi Anemia
- Seckel Syndrome

Strathdee CA, Gavish H, Shannon WR, Buchwald M.
Cloning of cDNAs for Fanconi's anaemia by functional complementation.
Nature. 1992 Apr 30;356(6372):763-7. Erratum in: Nature. 1992 Jul 30;358(6385):434.
Wang X, D'Andrea AD.
The interplay of Fanconi anemia proteins in the DNA damage response.
DNA Repair (Amst). 2004 Aug-Sep;3(8-9):1063-9. Review.
O'Driscoll M, Ruiz-Perez VL, Woods CG, Jeggo PA, Goodship JA.
A splicing mutation affecting expression of ataxia-telangiectasia and Rad3-related

protein (ATR) results in Seckel syndrome.
Nat Genet. 2003 Apr;33(4):497-501. Epub 2003 Mar 17.

Week 8: Diseases Associated with defects in non-homologous end joining

- LIG4 syndrome
- Severe Combined Immunodeficiency

O'Driscoll M, Gennery AR, Seidel J, Concannon P, Jeggo PA.
An overview of three new disorders associated with genetic instability: LIG4 syndrome, RS-SCID and ATR-Seckel syndrome.
DNA Repair (Amst). 2004 Aug-Sep;3(8-9):1227-35. Review.
O'Driscoll M, Cerosaletti KM, Girard PM, Dai Y, Stumm M, Kysela B, Hirsch B, Gennery A, Palmer SE, Seidel J, Gatti RA, Varon R, Oettinger MA, Neitzel H, Jeggo PA, Concannon P.
DNA ligase IV mutations identified in patients exhibiting developmental delay and immunodeficiency.
Mol Cell. 2001 Dec;8(6):1175-85.
Buck D, Malivert L, de Chasseval R, Barraud A, Fondaneche MC, Sanal O, Plebani A, Stephan JL, Hufnagel M, le Deist F, Fischer A, Durandy A, de Villartay JP, Revy P.
Cernunnos, a novel nonhomologous end-joining factor, is mutated in human immunodeficiency with microcephaly.
Cell. 2006 Jan 27;124(2):287-99.

Week 9: Diseases Associated with defective mismatch repair

- Hereditary nonpolyposis colon cancer
- Muir Torre Syndrome
- Turcot Syndrome

Peltomaki P.
Deficient DNA mismatch repair: a common etiologic factor for colon cancer.
Hum Mol Genet. 2001 Apr;10(7):735-40. Review.
Kruse R, Rutten A, Lamberti C, Hosseiny-Malayeri HR, Wang Y, Ruelfs C, Jungck M, Mathiak M, Ruzicka T, Hartschuh W, Bisceglia M, Friedl W, Propping P.
Muir-Torre phenotype has a frequency of DNA mismatch-repair-gene mutations similar to that in hereditary nonpolyposis colorectal cancer families defined by the Amsterdam criteria.
Am J Hum Genet. 1998 Jul;63(1):63-70. Erratum in: Am J Hum Genet 1998 Oct;63(4):1252.
Hamilton SR, Liu B, Parsons RE, Papadopoulos N, Jen J, Powell SM, Krush AJ, Berk T, Cohen Z, Tetu B, et al.
The molecular basis of Turcot's syndrome.
N Engl J Med. 1995 Mar 30;332(13):839-47.

Week 10: Diseases Associated with cell cycle response to DNA damage

- Li-Fraumeni Syndrome
- Hereditary Breast Cancer

Bell DW, Varley JM, Szydlo TE, Kang DH, Wahrer DC, Shannon KE, Lubratovich M, Verselis SJ, Isselbacher KJ, Fraumeni JF, Birch JM, Li FP, Garber JE, Haber DA.
Heterozygous germ line hCHK2 mutations in Li-Fraumeni syndrome.
Science. 1999 Dec 24;286(5449):2528-31.
Varley JM.
Germline TP53 mutations and Li-Fraumeni syndrome.
Hum Mutat. 2003 Mar;21(3):313-20. Review. Erratum in: Hum Mutat. 2003 May;21(5):551.

Nathanson KL, Wooster R, Weber BL.
Breast cancer genetics: what we know and what we need.
Nat Med. 2001 May;7(5):552-6. Review. Erratum in: Nat Med 2001 Jun;7(6):749. Nathanson KN [corrected to Nathanson KL].
Zhong Q, Chen CF, Li S, Chen Y, Wang CC, Xiao J, Chen PL, Sharp ZD, Lee WH.
Association of BRCA1 with the hRad50-hMre11-p95 complex and the DNA damage response.
Science. 1999 Jul 30;285(5428):747-50.
Sharan SK, Morimatsu M, Albrecht U, Lim DS, Regel E, Dinh C, Sands A, Eichele G, Hasty P, Bradley A.
Embryonic lethality and radiation hypersensitivity mediated by Rad51 in mice lacking Brca2.
Nature. 1997 Apr 24;386(6627):804-10

Week 11: Diseases Associated with defective DNA helicase function and involved in aging

- Bloom Syndrome
- Werner Syndrome
- Rothmund-Thomson Syndrome

Ellis NA, Groden J, Ye TZ, Straughen J, Lennon DJ, Ciocci S, Proytcheva M, German J.
The Bloom's syndrome gene product is homologous to RecQ helicases.
Cell. 1995 Nov 17;83(4):655-66.
Moser MJ, Oshima J, Monnat RJ Jr.
WRN mutations in Werner syndrome.
Hum Mutat. 1999;13(4):271-9. Review. Erratum in: Hum Mutat 1999;14(1):84-5.
Crabbe L, Jauch A, Naeger CM, Holtgreve-Grez H, Karlseder J.
Telomere dysfunction as a cause of genomic instability in Werner syndrome.
Proc Natl Acad Sci U S A. 2007 Feb 13;104(7):2205-10. Epub 2007 Feb 6.
Kitao S, Shimamoto A, Goto M, Miller RW, Smithson WA, Lindor NM, Furuichi Y.
Mutations in RECQL4 cause a subset of cases of Rothmund-Thomson syndrome.
Nat Genet. 1999 May;22(1):82-4.

Week 12: Genome instability/DNA repair and its role in cancer development and progression

Jefford CE, Irminger-Finger I.
Mechanisms of chromosome instability in cancers.
Crit Rev Oncol Hematol. 2006 Jul;59(1):1-14. Epub 2006 Apr 4. Review.
Eyfjord JE, Bodvarsdottir SK.
Genomic instability and cancer: networks involved in response to DNA damage.
Mutat Res. 2005 Dec 30;592(1-2):18-28. Epub 2005 Jul 5. Review.
Kops GJ, Weaver BA, Cleveland DW.
On the road to cancer: aneuploidy and the mitotic checkpoint.
Nat Rev Cancer. 2005 Oct;5(10):773-85. Review.
Thoms KM, Kuschal C, Emmert S.
Lessons learned from DNA repair defective syndromes.
Exp Dermatol. 2007 Jun;16(6):532-44. Review.