Draft syllabus for spring
2019 Freshman seminar - It's a mystery; understanding the "impossible"
Professor Craig Hunter, Department of Molecular and Cellular Biology

Students will experience the scientific method through reading, writing about, and discussing one or two primary research articles each week. Reading and open ended discussions will be supported by writing short (200-300 words) directed summaries prior to each class meeting. Goals include learning how to critically read and appreciate primary scientific literature, including the role of publication and culture on scientific investigation, and developing an appreciation for genetic and biochemical investigation of biological phenomena.

Provisional timeline:

Weeks 1-2 Mysterious observations
Weeks 3-4 Explanatory investigations
Weeks 5-7 Discovery of ancient (evolutionarily shared) pathways
Weeks 8-9 Applications
Weeks 10-12 origins, diversity, and functions

Mysterious observations

Week 1
Napoli C, Lemieux C, Jorgensen R (1990) Introduction of a chimeric chalcone synthase gene into petunia results in reversible co-suppression of homologous genes *in trans.* Plant Cell 2 279–289.

Guo S, Kempues KJ (1995) *par–1*, a gene required for establishing polarity in *C. elegans* embryos, encodes a putative ser/thr kinase that is asymmetrically distributed. *Cell* 81:611–620.

Week 2
Metzlaff M, O'Dell M, Cluster PD, Flavell RB (1997) RNA-mediated RNA degradation and chalcone synthase A silencing in petunia. Cell 88 845–854.

Timmons L, Fire A (1998) Specific interference by ingested dsRNA. *Nature*, 395:854.

H. Tabara, A. Grishok, C. C. Mello, title *Science* **282**, 430 (1998).

Explanatory investigations

Week 3
All students:
Fire A, Xu S, Montgomery MK, Kostas SA, Driver SE, Mello CC (1998) Potent and specific genetic interference by double-stranded RNA in Caenorhabditis elegans. *Nature* 1998, 391:806-811.

Group A students:
Montgomery MK, Xu S, Fire A: RNA as a target of double-stranded RNA-mediated genetic interference in Caenorhabditis elegans. *Proc Natl Acad Sci USA* 1998, 95:15502-15507.

Group B students:
Ngo H, Tschudi C, Gull K, Ullu E (1998) Double-stranded RNA induces mRNA degradation in *Trypanosoma brucei. Proc Natl Acad Sci USA* 95:14687-14692.

Group C students:
Waterhouse PM, Graham MW, Wang M: Virus resistance and gene silencing in plants can be induced by simultaneous expression of sense and antisense RNA. *Proc Natl Acad Sci USA* 1998, 95:13959-13964.

Week 4
Group A students:
Kennerdell JR, Carthew RW (1998) Use of dsRNA-mediated genetic interference to demonstrate that frizzled and frizzled 2 act in the wingless pathway. Cell 95 1017–1026

Group B students:
Tusch T, Zamore PA, Lehman R, Bartel DP, Sharp PA: Targeted mRNA degradation by double-stranded RNA *in vitro*. *Genes Dev* 1999, 13:3191-3197

Discovery

Week 5
Group A students:
Hamilton AJ, Baulcombe DC (1999) A species of small antisense RNA in posttranscriptional gene silencing in plants. *Science*, 286:950-952.

Group B students:
E. Bernstein, A. A. Caudy, S. M. Hammond, G. J. Hannon (2001) Role for a bidentate ribonuclease in the initiation step of RNA interference. *Nature* **409**, 363.

Group C students:
Zamore, P. D., Tuschl, T., Sharp, P. A. and Bartel, D. P. (2000). RNAi: double-stranded RNA directs the ATP-dependent cleavage of mRNA at 21 to 23 nucleotide intervals. Cell 101, 25–33.

Group D students:
Elbashir, S. M. et al (2001) RNA interference is mediated by 21- and 22- nucleotide RNAs. Genes Dev. 15, 188–200

Week 6
all students:
Tabara H, Sarkissian M, Kelly WG, Fleenor J, Grishok A, Timmons L, Fire A, Mello CC (1999) The *rde-1* gene, RNA interference, and transposon silencing in *C. elegans*. *Cell* 99:123-132.

Group A students:
Hammond, S. M. et al. (2001) Argonaute2, a link between genetic and biochemical analyses of RNAi. Science 293:1146–1150.

Group B students:
Cogoni C, Macino G (1999) Gene silencing in Neurospora crassa requires a protein homologous to RNA-dependent RNA polymerase. *Nature* 399:166-169.

Group C students:
Cogoni C, Macino G (1999) Posttranscriptional gene silencing in *neurospora* by a RecQ DNA helicase. *Science*, 286:2342-2344.

Group D students:

Tabara, H., Yigit, E., Siomi, H. and Mello, C. C. (2002). The dsRNA binding protein RDE-4 interacts with RDE-1, DCR-1, and a DExH-box helicase to direct RNAi in C. elegans. Cell 109, 861–871.

Week 7
all students:
W. M. Winston, C. Molodowitch, C. P. Hunter (2002) Systemic RNAi in C. elegans requires the putative transmembrane protein SID-1. *Science* **295**, 2456

Group A students:

O. Voinnet, C. Lederer, D. C. Baulcombe (2000) A viral movement protein prevents spread of the gene silencing signal in Nicotiana benthamiana. ***Cell*** **103, 157.**

Group B students:
Winston, W. M., Sutherlin, M., Wright, A. J., Feinberg, E. H. and Hunter, C.P. (2007). Caenorhabditis elegans SID-2 is required for environmental RNA interference. Proceedings of the National Academy of Sciences, USA, 104, 10565–10570. doi: 0611282104 [pii] 10.1073/pnas.0611282104.

Applications

Week 8
Carpenter, A. E. and Sabatini, D. M. (2004). Systematic genome-wide screens of gene function. Nature Reviews Genetics 5, 11–22

Ashrafi, K. et al. (2003) Genome-wide RNAi analysis of Caenorhabditis elegans fat regulatory genes. Nature 421, 268–272

Lee, S.S. et al. (2003) A systematic RNAi screen identifies a critical role for mitochondria in C. elegans longevity. Nat. Genet. 33, 40–48

Reddien, P.W. et al. (2005) Identification of genes needed for regeneration, stem cell function, and tissue homeostasis by systematic gene perturbation in planaria. Dev. Cell 8, 635–649

Week 9:
Schott DH, Cureton DK, Whelan SP, Hunter CP (2005) *Proc Natl Acad Sci USA* 102:18420 – 18424.

Baum JA, Bogaert T, Clinton W, Heck GR, Feldmann P, Ilagan O, Johnson S, Plaetinck G, Munyikwa T, Pleau M, et al (2007) Control of coleopteran insect pests through RNA interference. Nat Biotechnol 25 1322–1326

origins, diversity, functions

Week 10:
Lee, R. C., Hammell, C. M. and Ambros, V. (2006). Interacting endogenous and exogenous RNAi pathways in Caenorhabditis elegans. RNA 12, 589–597.

Pak, J. and Fire, A. (2007). Distinct populations of primary and secondary effectors during RNAi in C. elegans. Science 315, 241–244.

Yigit, E., Batista, P. J., Bei, Y., Pang, K. M., Chen, C. C., Tolia, N. H., Joshua-Tor, L., Mitani, S., Simard, M. J. and Mello, C. C. (2006). Analysis of the C. elegans Argonaute family reveals that distinct Argonautes act sequentially during RNAi. Cell 127, 747–757.

Guang, S., Bochner, A. F., Pavelec, D. M., Burkhart, K. B., Harding, S., Lachowiec, J. and Kennedy, S. (2008). An Argonaute transports siRNAs from the cytoplasm to the nucleus. Science, 321(5888), 537–541.

Guang, S., Bochner, A. F., Burkhart, K. B., Burton, N., Pavelec, D. M. and Kennedy, S. (2010). Small regulatory RNAs inhibit RNA polymerase II during the elongation phase of transcription. Nature 465, 1097–1101.

Minkina O, Hunter CP. Stable Heritable Germline Silencing Directs Somatic Silencing at an Endogenous Locus. Mol Cell. 2017 Feb 16;65(4):659-670.e5.

Schott D, Yanai I, Hunter CP. Natural RNA interference directs a heritable response to the environment. Sci Rep. 2014 Dec 9;4:7387.