TBMH 5004
Fundamentals of TBMH

Christopher Wetherill
Virginia Polytechnic Institute and State University

Contents

Part I
General Overview

---

1 TBMH Fundamentals Overview

For the purpose of this course and program, translational biology is the act or process of changing some aspects of knowledge about living organisms and vital processes. Notably, the translational element of this program does not specifically apply to either medicine or health.

1.1 Translational Research

Although the definition and stages of translational research vary, we will define it in five stages, broadly, as:

1. **T0** — The focus is on identifying problems, opportunities, and novel approaches to tackle those problems and opportunities. This is characterizes by the identification of approaches to relevant health problems with research beginning with a basic research question.
2. **T1** — Discovery or foundational research and development of treatments. This is translational research in which findings are moved from basic research to testing for clinical effect and/or applicability.
3. **T2** — Health application to assess efficacy of treatment. This research assesses the value of the treatment in a clinical trial (i.e., in Phase III clinical trials).
4. **T3** — Health practice; science of dissemination and implementation. This attempts to move evidence-based guidelines into health practice (analogous to Phase IV clinical trials).
5. **T4** — Evaluation of health impact on real-world populations. This is, broadly, outcomes research that monitors the morbidity, mortality, benefits, and risks in the population of the treatment.

Specifically, this is an iterative process with each stage building on and informing every other.

1.2 Clinical Trials

The phases of clinical trials are as follow (via the NIH):

1. **Phase I** — Researchers test a new drug or treatment in a small group for the first time to evaluate its safety, determine its dosage range, and identify side effects.
2. **Phase II** — The drug or treatment is given to a larger group of people to see if it is effective and to further evaluate its safety.
3. **Phase III** — The drug or treatment is given to large groups of people to confirm its effectiveness, monitor side effects, compare it to commonly-used treatments, and collect information that will allow the drug to be used safely.
4. **Phase IV** — Studies done after the drug is places on the market to gather information on its effect in varied populations and any side effects associated with long-term use.

2 Fragile X Syndrome

2.1 Overview

Fragile X Syndrome (also known as Martin-Bell syndrome, or Escalante's syndrome) is a sex-linked genetic disorder causing mental retardation and one of the largest single-gene causes of autism among children.

Specifically, Fragile X Syndrome (FX) is most often caused by a simple CGG repeat in the FMR1 gene on the X chromosome. This, in turn, causes an under-expression of the Fragile X mental retardation protein (FMRP). The amount of FRMP present is demonstrated to affect synaptic plasticity (with an abundance correlating to increased plasticity), and thereby to affect learning. As such, when the protein is absent, there is reduced plasticity in the individual, yielding mental retardation. The degree of retardation is inversely proportional to the amount of FMRP present in the individual.

Moreover, research has indicated in mouse models that there is a functional opposition between FMRP and certain metabotropic glutamate receptors (mGluRs), and specifically mGluR5. FMRP and mGluR5 both appear to regulate mRNA translation at the synapse, with mGluR5 inhibiting translation and FMRP promoting it. As such, in the absence of FMRP, mRNA translation at the synapse is highly downregulated, resulting in the observed mental retardation. (Specifically, mGluR5 inhibits the growth of glutamate receptors on, and decreases the number embedded in, the postsynaptic membrane. Hereby, the dendritic spine's sensitivity is reduced and long-term depression is achieved.)

In neonates, long-term potentiation (LTP) appears to be important for retaining newly-formed synapses and long-term depression (LTD) for activity-guided synapse elimination. Further, post-synaptic group 1 mGluR activation is responsible in many parts of the brain for LTD. However, for this to occur, there must be a rapid translation of preëxisting mRNA in the postsynaptic dendrites. Given that FMRP mRNA is found in dendrites and that FMRP binds mRNA, it is perhaps unsurprising that in the absence of FMRP (in FMR1 knockout mice), exaggerated protein-synthesis-dependent LTD has been observed.

"According to this model, mGluR activation normally stimulates synthesis of proteins involved in stabilization of LTD and, in addition, FMRP. The FMRP functions to inhibit further synthesis (an example of end-product inhibition), and puts a brake on LTD" (Bear, Huber, & Warren). That is, in a typical individual, FMRP acts as a negative feedback to LTD, thus promoting normal growth. When it is absent, however, LTD is allowed to continue unimpeded, resulting in excessive activity-guided synapse elimination. This interaction between FMRP and mGluRs may thus result both in an insufficient number of synaptic interconnections at birth (via synaptic pruning) and an inability to effectively form these connections throughout life (via reduced synaptic plasticity resulting from mGluR-induced LTD).

2.2 Synaptic Neurobiology

Some select receptors:

1. AMPAR — ligand-gated ion channel (glutamate binds to AMPA, sodium and potassium are conducted along their electrochemical gradient)
2. NMDAR — highly permeable to calcium; ionotropic receptor
3. mGluR — second messenger-linked (metabotropic) receptor

3 Age-Related Macular Degeneration

3.1 Overview

Possession of one or more chronic disease or disorder has been found (Moussavi, 2007) to significantly correlate with an elevated prevalence of depression. Significantly higher likelihood for comorbid depression is found among those with multiple chronic disorders. Moreover, visually-limiting eye disease specifically is significantly correlated with an increased risk of comorbid depression among adults (Popescu et al., 2012). Among those with visually-limiting eye disease, an integrated mental health and low vision intervention may significantly reduce the risk of comorbid depression (Rovner et al., 2014).

Age-related macular degeneration (AMD) is an age-related disease characterized by the loss of vision in the center of the visual field (i.e., the macula lutea). It has both dry and wet forms. In the dry form, cellular debris accumulates between the retina and the choroid and may cause the retina to detach. In the wet form, blood vessels in the choroid grow abnormally and occlude vision. "The disease pathology emerges with the degeneration of macula which forms the central part of retina. The macula consists of photoreceptor (rods and cones) important for central vision" (Sharma, Sharma, & Anand, 2014).

Several age-related cellular processes have been identified as potential disruptors to ocular homeostasis, including:

1. metabolic pathways (Uchiki et al., 2012);
2. telomere shortening;
3. impaired mechanism of autophagy;
4. disrupted proteolytic and lysosomal function (Viiri et al., 2013);
5. decline in ability to combat oxidative stress (Cutler et al., 2004); and
6. enhanced mitochondrial dysfunction.

The emergence of AMD arises from a complex interaction of both environmental (e.g., smoking, IV-B exposure) and genetic (e.g., immune system components, angiogenic factors) that is not yet fully understood. "Clinical trials have shown that VEGF [vascular endothelial growth factor] antagonists provide major benefits for patients with subretinal NV [neovascularization] due to AMD and even greater benefits are seen by combining antagonists of VEGF and PDGF-B [platelet-derived growth factor-B]" (Campochiaro, 2013). Additionally, *in vivo* research (using non-viral gene therapy) by Iriyama et al. (2011) has shown promise for reversing the effects of choroidal neovascularization by transfection of soluble fms-like tyrosine kinase-1 (sFlt-1) with the polyion complex (PIC) micelle encapsulating DNA.

4 Hepatitis C

4.1 Overview

Part II
Cancer

Part III
Neuroscience

Part IV
Immunity and Infectious Disease

Part V
Health Implementation Science

Part VI
Metabolic and Cardiovascular Science

Part VII
Development, Aging, and Repair

References

Adams, C. P., & Brantner, V. V. (2006). Estimating the cost of new drug development: Is it really $802 million? *Health Affairs*, *25*(2), 420-428. Retrieved from http://content.healthaffairs.org/content/25/2/420.abstract doi: 10.1377/hlthaff.25.2.420

Bagni, C., Tassone, F., Neri, G., & Hagerman, R. (2012, 12). Fragile x syndrome: causes, diagnosis, mechanisms, and therapeutics. *The Journal of Clinical Investigation*, *122*(12), 4314-4322. Retrieved from http://www.jci.org/articles/view/63141 doi: 10.1172/JCI63141

Bear, M. F., Huber, K. M., & Warren, S. T. (2004). The mglur theory of fragile x mental retardation. *Trends in Neurosciences*, *27*(7), 370 - 377. Retrieved from http://www.sciencedirect.com/science/article/pii/S0166223604001328 doi: http://dx.doi.org/10.1016/j.tins.2004.04.009

Berry-Kravis, E. (2014). Mechanism-based treatments in neurodevelopmental disorders: Fragile x syndrome. *Pediatric Neurology*, *50*(4), 297 - 302. Retrieved from http://www.sciencedirect.com/science/article/pii/S0887899413007157 doi: http://dx.doi.org/10.1016/j.pediatrneurol.2013.12.001

Bichoupan, K., Martel-Laferriere, V., Sachs, D., Ng, M., Schonfeld, E. A., Pappas, A., ... Branch, A. D. (2014). Costs of telaprevir-based triple therapy for hepatitis c: $189,000 per sustained virological response. *Hepatology*. Retrieved from http://dx.doi.org/10.1002/hep.27340 doi: 10.1002/hep.27340

Campochiaro, P. (2013). Ocular neovascularization. *Journal of Molecular Medicine*, *91*(3), 311-321. Retrieved from http://dx.doi.org/10.1007/s00109-013-0993-5 doi: 10.1007/s00109-013-0993-5

Dolen, G., & Bear, M. F. (2005). Courting a cure for fragile x. *Neuron*, *45*(5), 642 - 644. Retrieved from http://www.sciencedirect.com/science/article/pii/S0896627305001649 doi: http://dx.doi.org/10.1016/j.neuron.2005.02.021

Dolen, G., Carpenter, R. L., Ocain, T. D., & Bear, M. F. (2010). Mechanism-based approaches to treating fragile x. *Pharmacology & Therapeutics*, *127*(1), 78 - 93. Retrieved from http://www.sciencedirect.com/science/article/pii/S0163725810000586 doi: http://dx.doi.org/10.1016/j.pharmthera.2010.02.008

Emmert-Buck, M. (2014). Translational research: From biological discovery to public benefit (or not). *Advances in Biology*, *2014*.

Fang, F., & Casadevall, A. (2009). Lost in translation—basic science in the era of translational research. *Infection and Immunity*, *78*, 563-566.

Goldblatt, E., & Lee, W. (2010). From bench to bedside: the growing use of translational research in cancer medicine. *American Journal of Translational Research*, *2*, 1-18.

Iliff, A. J., Renoux, A. J., Krans, A., Usdin, K., Sutton, M. A., & Todd, P. K. (2013). Impaired activity-dependent fmrp translation and enhanced mglur-dependent ltd in fragile x premutation mice. *Human Molecular Genetics*, *22*(6), 1180-1192. Retrieved from http://hmg.oxfordjournals.org/content/22/6/1180.abstract doi: 10.1093/hmg/dds525

Iriyama, A., Oba, M., Ishii, T., Nishiyama, N., Kataoka, K., Tamaki, Y., & Yanagi, Y. (2011, 12). Gene transfer using micellar nanovectors inhibits choroidal neovascularization in vivo. *PLoS ONE*, *6*(12), e28560. doi: 10.1371/journal.pone.0028560

Kohli, A., Shaffer, A., Sherman, A., & Kottilil, S. (2014). Treatment of hepatitis c: A systematic review. *JAMA*, *312*(6), 631-640. Retrieved from http://dx.doi.org/10.1001/jama.2014.7085 doi: 10.1001/jama.2014.7085

Kraft, A. (2013). Translational medicine: The future of therapy. In J. Mittra & C. Milne (Eds.), (p. 19-53). Pan Stanford.

Levenga, J., de Vrij, F. M., Oostra, B. A., & Willemsen, R. (2010). Potential therapeutic interventions for fragile x syndrome. *Trends in Molecular Medicine*, *16*(11), 516 - 527. Retrieved from http://www.sciencedirect.com/science/article/pii/S1471491410001267 doi: http://dx.doi.org/10.1016/j.molmed.2010.08.005

MacLachlan, T. K., Lukason, M., Collins, M., Munger, R., Isenberger, E., Rogers, C., ... Wadsworth, S. (2011). Preclinical safety evaluation of aav2-sflt01— a gene therapy for age-related macular degeneration. *Molecular Therapy*, *19*(2), 326-334.

Moussavi, S., Chatterji, S., Verdes, E., Tandon, A., Patel, V., & Ustun, B. (2007). Depression, chronic diseases, and decrements in health: results from the world health surveys. *The Lancet*, *370*(9590), 851 - 858. Retrieved from http://www.sciencedirect.com/science/article/pii/S0140673607614159 doi: http://dx.doi.org/10.1016/S0140-6736(07)61415-9

Osterweil, E. K., Krueger, D. D., Reinhold, K., & Bear, M. F. (2010). Hypersensitivity to mglur5 and erk1/2 leads to excessive protein synthesis in the hippocampus of a mouse model of fragile x syndrome. *The Journal of Neuroscience*, *30*(46), 15616-15627. Retrieved from http://www.jneurosci.org/content/30/46/15616.abstract doi: 10.1523/JNEUROSCI.3888-10.2010

Popescu, M. L., Boisjoly, H., Schmaltz, H., Kergoat, M.-J., Rousseau, J., Moghadaszadeh, S., ... Freeman, E. E. (2012). Explaining the relationship between three eye diseases and depressive symptoms in older adults. *Investigative Ophthalmology & Visual Science*, *53*(4), 2308-2313. Retrieved from http://www.iovs.org/content/53/4/2308.abstract doi: 10.1167/iovs.11-9330

Popp, N., Chu, X. K., Shen, D., Tuo, J., & Chan, C.-C. (2013). Evaluating potential therapies in a mouse model of focal retinal degeneration with age-related macular degeneration (amd)-like lesions. *Journal of Clinical and Experimental Opthalmolgy*, *4*(5).

Rovner, B. W., Casten, R. J., Hegel, M. T., Massof, R. W., Leiby, B. E., Ho, A. C., & Tasman, W. S. (2014). Low vision depression prevention trial in age-related macular degeneration: A randomized clinical trial. *Ophthalmology*. Retrieved from http://www.sciencedirect.com/science/article/pii/S0161642014004229 doi: http://dx.doi.org/10.1016/j.ophtha.2014.05.002

Sagnelli, E., Santantonio, T., Coppola, N., Fasano, M., Pisaturo, M., & Sagnelli, C. (2014). Acute hepatitis c: clinical and laboratory diagnosis, course of the disease, treatment. *Infection*, *42*(4), 601-610. Retrieved from http://dx.doi.org/10.1007/s15010-014-0608-2 doi: 10.1007/s15010-014-0608-2

Scheel, T. K. H., & Rice, C. M. (2013). Understanding the hepatitis c virus life cycle paves the way for highly effective therapies. *Nature Medicine*, *19*(7), 837-849.

Seely, E., & Grinspoon, S. (2009). Clinical and translational science: Principles of human research. In D. Robertson & G. Williams (Eds.), (p. 3-12). Academic Press.

Sharma, K., Sharma, N. K., & Anand, A. (2014). Why amd is a disease of ageing and not of development: mechanisms and insights. *Frontiers in Aging Neuroscience*, *6*(151). doi: 10.3389/fnagi.2014.00151

Index