




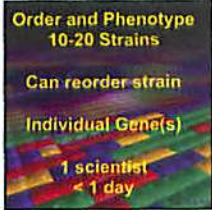
What is my message?



- Computational genetic analyses in mice enable translatable genetic discoveries
 - Narcotic Drug Addiction**
 - Neuropathic Pain**
- Integrative approaches for analysis of complex pathobiology
 - Acetaminophen Toxicity**
 - Narcotic Drug Responses**

Computational Tools Accelerate the Pace of Genetic Discovery

"You can't possibly do that" 

QTL Analysis	Computational Analysis
Produce, Genotype and Phenotype 200–1000 F2 Each F2 is unique Analyze 10-70 Mb 3-5 scientists 3-10 years	 Order and Phenotype 10-20 Strains Can reorder strain Individual Gene(s) 1 scientist < 1 day

5-HT Receptors

- Serotonin (5HT)
 - Mood, cognition, circadian rhythm, pain...
 - Synthesis: Raphe, midbrain & pons
- 5HT3 Receptor: (one of 7 families)
 - Ligand-gated ion channel: 5 subunits
 - Antagonists: close Agonists: open
 - Modulate transmitter release: DA, GABA, 5HT
 - Cortex, amygdala, nucleus accumbens

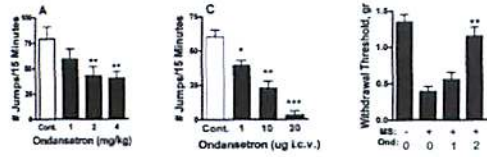
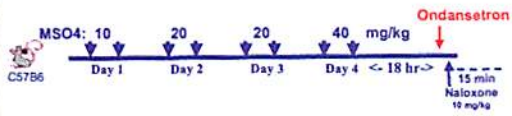


- 5HT3 Antagonist
- Chemotherapy-induced nausea
- Well tolerated with few side effects



Ondansetron (Zofran)
FDA approved: 01/91
8 mg bid or tid

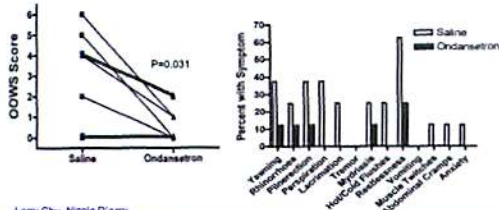
5-HT3a Receptor & Narcotic Dependence??



David Clark

Acute Experimental Morphine Withdrawal in Human Subjects

Randomized, double-blinded, placebo-controlled, crossover study



Larry Chu, Nicole D'arcy

5HT3a & Narcotic Drug Addiction

- Genetic Analysis -> Novel Solution for dependence & withdrawal
- 5HT3 Antagonists effective in mouse & man
- 'Medical Vaccination' to remedy an iatrogenic problem



Pharmacogenetics and Genomics 19:153, 2009

Genetic Analysis: Incisional Wound Biology

Full Thickness Skin Incision:
16 Strains, 24 hr

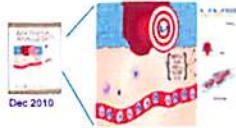


Analyze 16 Cytokines
mRNA Profile: 39K Genes

Haplotype-Based Genetic Analysis

Select candidate gene(s)

Experimental Analysis
-in vitro & in vivo mouse
-Human surgical incisions
and sunburns



New model: IL-1 regulates the production of multiple inflammatory mediators

Perioperative IL-1 inhibition can reduce post-surgical pain and inflammation

Clinical Trial begun at Stanford 2011:
Will perioperative administration of an IL-1 inhibitor reduce incisional pain?

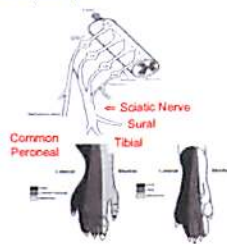
Spared Nerve Injury (SNI) a rodent model of chronic pain

- Partial sciatic nerve injury is a model for neuropathic pain

- Ligate 2 branches of Sciatic Nerve
- Sural nerve is 'spared'

- Rapid (<24 hr), prolonged (> 6 month) changes in the Sural N. distribution:

- Mechanical hypersensitivity
- Hyperalgesia
- Cold allodynia
- Heat hyperalgesia



Pain 87:149, 2000

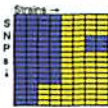
P2rx7 & Chronic Pain

- P2rx7 allelic differences alter
 - Experimental pain response in mice
 - Chronic pain in humans
- P2rx7 pore formation (but not channel function) is key
 - Peptides active in spinal cord-DRG
- Enable 'Personalized Pain Medicine'
 - Rx: target pore formation
 - Dx: individuals with responsive alleles

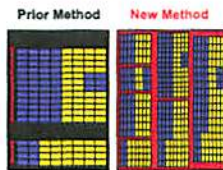


'Next Generation' Computational Genetic Mapping

Whole Genome SNP dB
Use genome sequence
~12M SNPs per strain



New Block Construction Method
Reduces false negatives



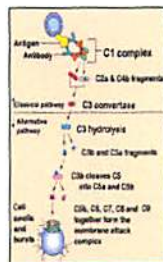
Dynamic Block Construction
30K-fold faster
Customized & 'real time'

Infection and Immunity, In Press

David Dill and Ming Zheng

Murine Models of Candida Albicans Infection

- Comensal fungus
 - 96% of fungal infections in immunocompromised pts
 - 47% mortality in ICU patients
- Mimics human infection
 - Brain & kidney are target organs
 - Death results from kidney failure
- Complement has a well defined role
 - C5 deficient mice have poor survival
 - 50% of strains are C5 deficient



...but, C5 is not the whole story!

Infection and Immunity in press 2011

