

# Pain Advances

- Who is the intended audience for these advances?
- How should they be presented?
  - Publications/papers with brief relevance statements?
  - A more informative summary of the significance and likely contribution of each advance?
- Should we try to balance them thematically?
- How many should initially be posted online?
- How often should the list be updated?

# Voting Summary

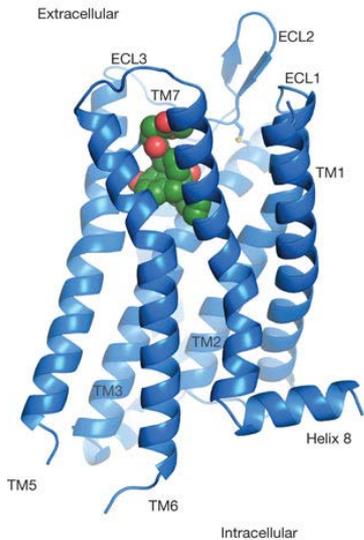
- 131 advances initially submitted
- 20 advances selected by 11 IPRCC members last week
  - Several advances had multiple votes
  - 3 ongoing studies were also highlighted by members
- We arranged a preliminary thematic categorization:
  - Molecular
  - Systems neuroscience
  - Specific conditions and special populations
  - Therapeutics
  - Population-based studies

# Molecular

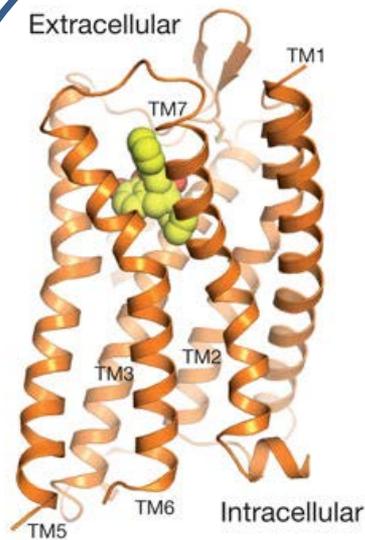
- (+)-Naloxone, an opioid-inactive Toll-Like Receptor 4 signaling inhibitor, reverses multiple models of chronic neuropathic pain in rats
- Resolvins RvE1 and RvD1 attenuate inflammatory pain via central and peripheral actions
- Piezo proteins are pore-forming subunits of mechanically activated channels
- The role of *Drosophila* Piezo in mechanical nociception
- Structure of the  $\delta$ -opioid receptor bound to naltrindole

# Crystal Structures of 4 Opioid Receptors Solved this Year

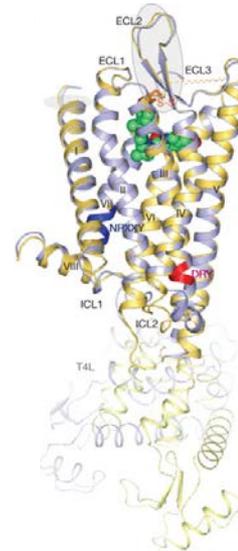
- Solving opioid receptor structures is essential for discovery of novel opioids that still relieve pain but have less potential for abuse.
- These receptors had long been intractable to X-ray crystallography, and trans-NIH investment was needed to develop these new cutting-edge techniques



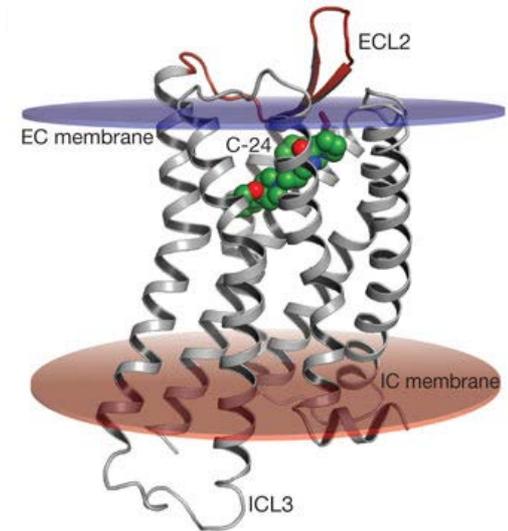
$\mu$ -opioid receptor  
A Manglik *et al. Nature*  
**485**, 321-6 (2012)



$\delta$ -opioid receptor  
S Granier *et al. Nature*  
**485**, 400-4 (2012)



$\kappa$ -opioid receptor  
H Wu *et al. Nature*  
**485**, 327-32 (2012)

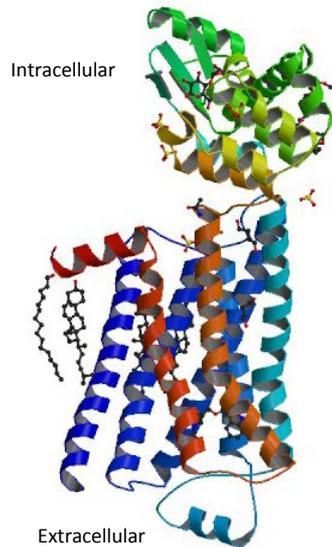


N/OFQ receptor  
A Thompson *et al. Nature*  
**485**, 395-9 (2012)

# 2012 Nobel Prize in Chemistry

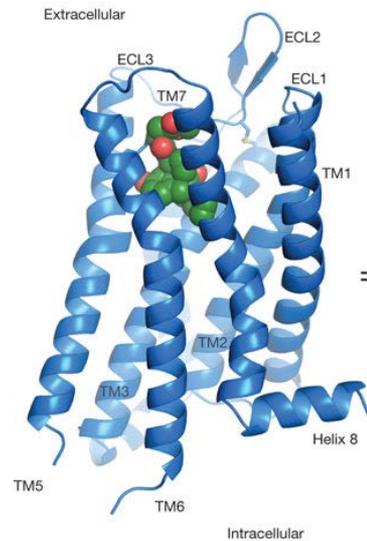


- Robert Lefkowitz and Brian Kobilka  
for studies of **G-protein-coupled receptors**
- *"About half of all medications, including beta blockers, antihistamines and various kinds of psychiatric medications, act through these receptors."* - NIH Director Francis S. Collins
- Both winners are NIH grantees



$\beta_2$ -adrenergic receptor

V Cherezov *et al.*  
*Science* **318** (2007)



$\mu$ -opioid receptor

A Manglik *et al.*  
*Nature* **485** (2012)

# Systems Neuroscience

- Forebrain GABAergic neuron precursors integrate into adult spinal cord and reduce injury-induced neuropathic pain
- Corticostriatal functional connectivity predicts transition to chronic back pain
- Towards a physiology-based measure of pain: patterns of human brain activity distinguish painful from non-painful thermal stimulation

# Specific Conditions and Special Populations

- Increasing prevalence of knee pain and symptomatic knee osteoarthritis
- Relationship between vulvodynia and chronic comorbid pain conditions
- Cancer-related chronic pain: Examining quality of life in diverse cancer survivors
- Chronic musculoskeletal pain and the occurrence of falls in an older population
- Racial and ethnic disparities in pain: causes and consequences of unequal care
- Sex differences in reported pain across 11,000 patients captured in electronic medical records
- Sex, gender, and pain: A review of recent clinical and experimental findings

# Translation, Therapeutics and Treatment

- Truncated G protein-coupled  $\mu$ -opioid receptor MOR-1 splice variants are targets for highly potent opioid analgesics lacking side effects
- Acute augmentation of epoxygenated fatty acid levels rapidly reduces pain-related behavior in a rat model of type I diabetes
- Gene therapy for pain: Results of a Phase I clinical trial
- Spinal manipulation, medication, or home exercise with advice for acute and subacute neck pain
- Emergency department visits attributed to selected analgesics, United States, 2004-2005

# Initiatives and Population-Based Studies

- ACTION/IMPACT

(Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks / Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials)

- MAPP Network

(Multi-Disciplinary Approach to the Study of Chronic Pelvic Pain)

- OPERA study

(Orofacial Pain: Prospective Evaluation and Risk Assessment)

# Interagency Autism Coordinating Committee – Summary of Advances

- Annual process
- IACC nominates ~60 peer-reviewed

The Interagency Autism Coordinating Committee

## Articles Selected for the 2011 Summary of Advances

### Question 1: When Should I Be Concerned?

**Disrupted neural synchronization in toddlers with autism** – Dinstein I, Pierce K, Eyster L, Solso S, Malach R, Behrmann M, Courchesne E. *Neuron*. 2011 Jun 23;70(6):1218-25. [[PMID: 21689606](#)]

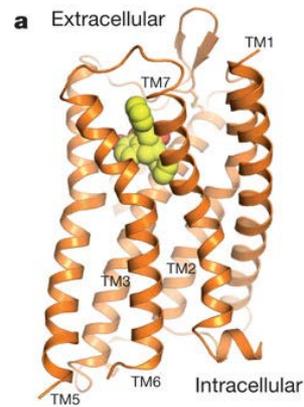
A study of sleeping toddlers identified patterns of abnormal neural activity that could aid in the early diagnosis of autism and help to understand underlying causes. Using functional magnetic resonance imaging (fMRI), researchers found that 72 percent of children with ASD showed decreased synchronization across brain hemispheres in areas commonly associated with language and communication. This decreased synchronization was rarely seen in typically developing children, or those with delayed language development who did not have autism. Strong synchronization between the right and left hemisphere of the brain is critical for proper functioning, and there is evidence of disrupted synchronization in neurological disorders such as schizophrenia and Alzheimer's disease. While disrupted synchronization has been documented in adults with autism, researchers had been unable to study the phenomenon in early childhood because toddlers cannot remain still long enough to undergo a brain scan when awake. Researchers were able to overcome this challenge by performing scans on sleeping children; neurons remain synchronized between regions of the brain with similar function even while resting. The brain scans revealed that weak neural synchronicity is evident in the early stages of autism and that the strength of synchronization is linked to the degree of the child's symptoms – children with the weakest neural synchronization exhibit the most severe impairments. The researchers note that measures of neural synchronization could one day play a role in early autism diagnosis, particularly because the measure can be taken while the child sleeps.

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# A Molecular Advance

## Structure of the $\delta$ -opioid receptor bound to naltrindole

Granier et al. *Nature* 485, 400-4 (2012)



- Opioids like morphine are commonly prescribed to patients to relieve pain. However, opioids cause many undesirable side effects and have the potential to be abused. Scientists are studying how to design new opioids that still relieve pain but have less potential for side effects and abuse, as such drug discovery would transform the field of pain medicine. This effort requires an understanding of the structure of the receptors that opioids interact with in the brain to relieve pain. These receptors are of a particularly complex type called G-protein coupled receptors (GPCRs), and their structures had long been impossible to study in the lab. However, the structures of the four known opioid receptors were all published this year in the journal *Nature*. Brian Kobilka, a contributor to this work, won the Nobel Prize in Chemistry last week for his work (with Robert Lefkowitz) on how GPCRs function in the body.

# **IACC: Seven Critical Questions Asked by People and Families Living with ASD:**

- Question 1: When Should I Be Concerned?
- Question 2: How Can I Understand What Is Happening?
- Question 3: What Caused This To Happen And Can This Be Prevented?
- Question 4: Which Treatments and Interventions will Help?
- Question 5: Where Can I Turn for Services?
- Question 6: What Does the Future Hold, Particularly for Adults?
- Question 7: What Other Infrastructure and Surveillance Needs Must Be Met?