

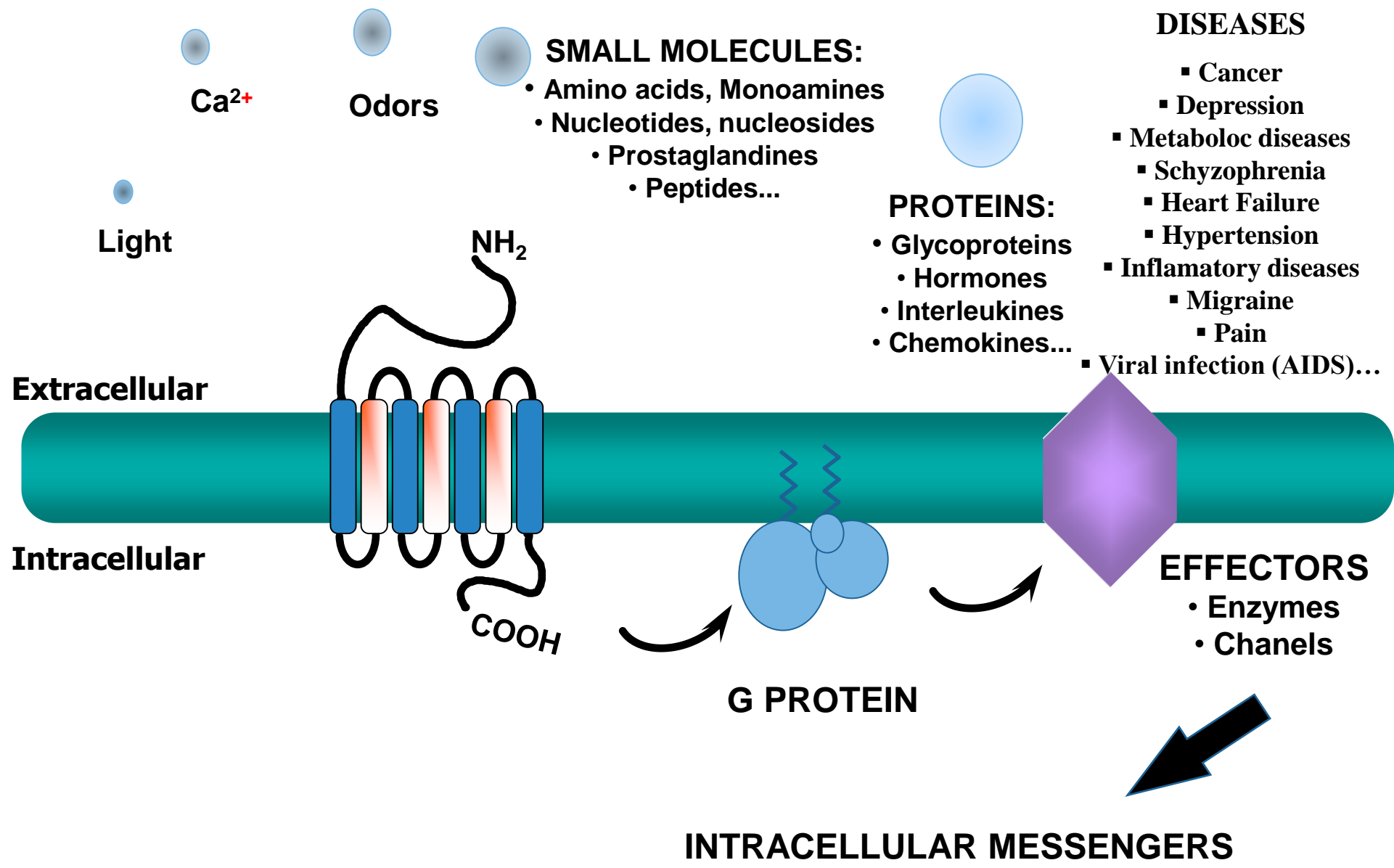


illuminating the Life of G protein Coupled Receptors

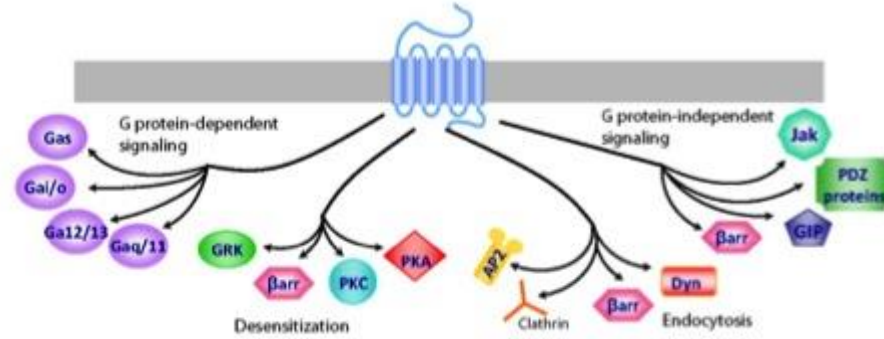
Michel Bouvier, Stephane Laporte, Graciela Pineyro, Richard Leduc, Terry Hébert, Christian Le Guill
Université de Montréal, Université McGill, MUCH, Ste-Justine Hospital, Université de Sherbrooke



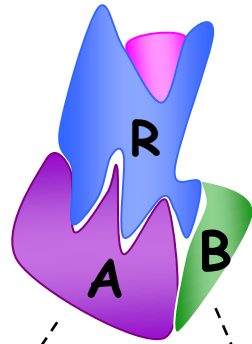
G Protein-Coupled Receptors



Functional Selectivity & Ligand-Biased Signalling



Ligand 1

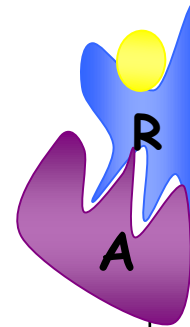


Pathway A

Pathway B

Moderate efficacy
Developing Tolerance

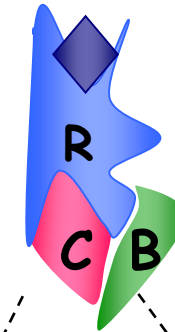
Ligand 2



Pathway A

High Therapeutic Efficacy

Ligand 3



Pathway C

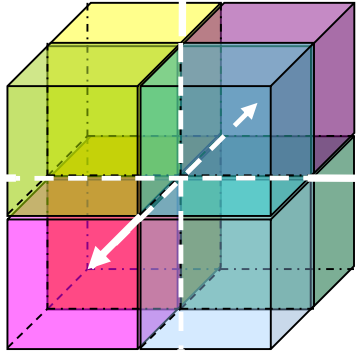
Pathway B

Adverse Effects

GPCR Functional Selectivity Relevant for Drug Discovery

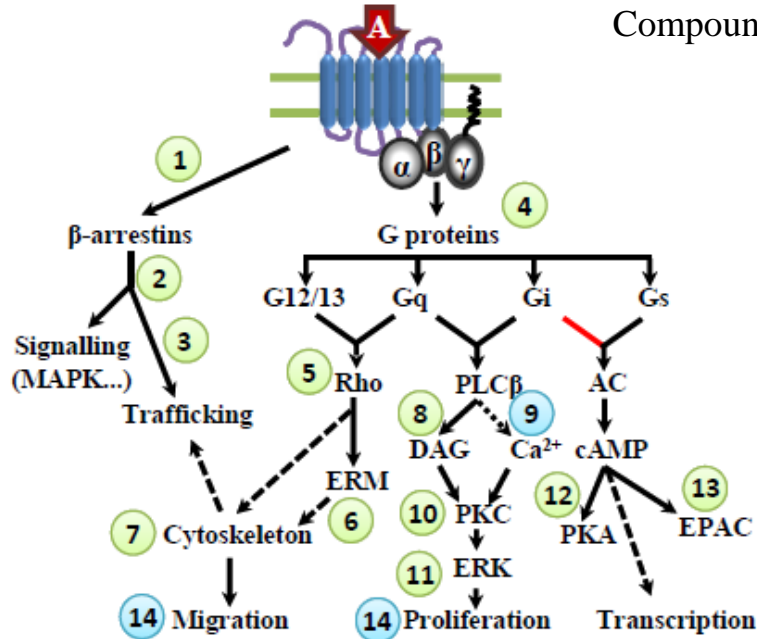
Receptors	Biological Outcomes		
AT ₁ R Biased Ago	increased Cardiac contractility Anti-fibrotic	Fluid + Na retention	Increased blood pressure
PAR ₂ Biased Antago	Anti- inflammation Analgesia	Constipation	Inhibits wound healing
MOR Biased Ago	Analgesia	Constipation	Respiratory depression
GLP ₁ Biased Ago	pro-Insulin secretion	Gastric emptying	Nausea
Ghrelin Biased Ago	pro-Insulin secretion	Gastric emptying	Nausea
FPR ₂ Biased Antago	Inflammation resolution		pro- inflammatory

The challenge and the Proposed Solution



The number of compound with distinct efficacy profiles (C) increases exponentially with the number of read out considered (n)

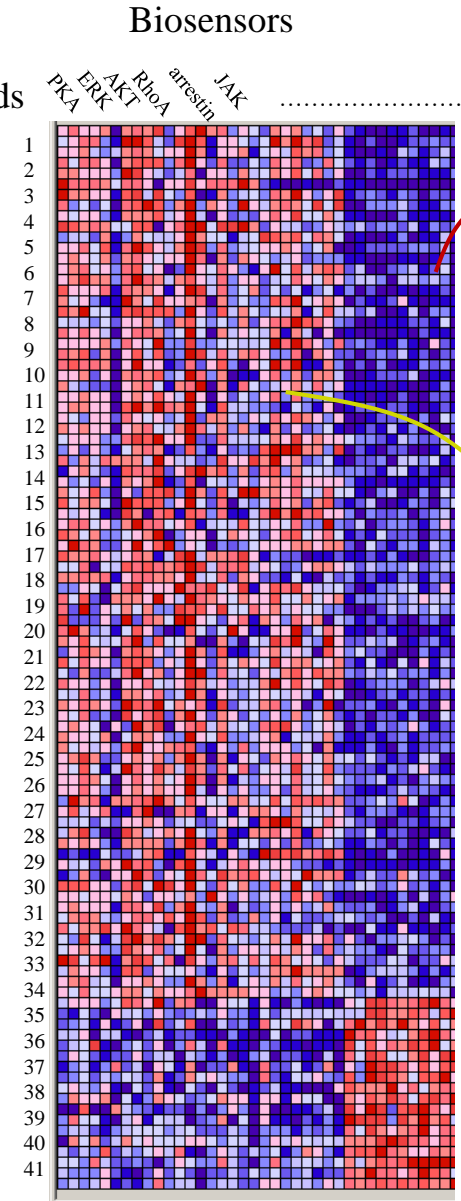
$$C = 2^n$$



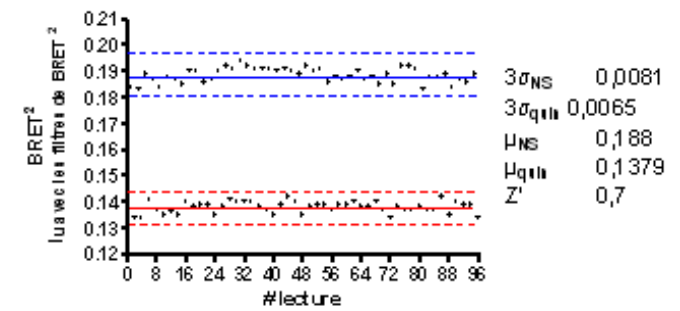
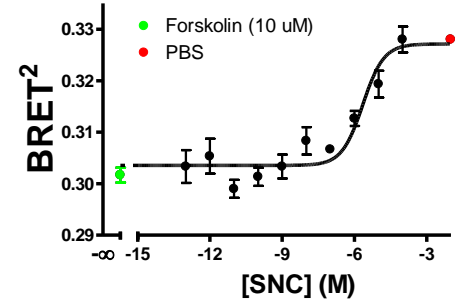
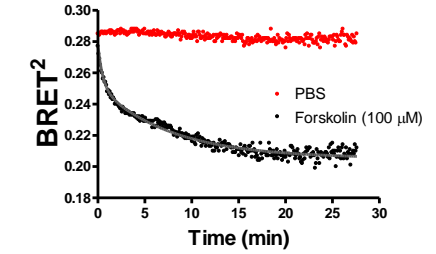
Gs G12 RhoA cAMP βArr Etc...



Compounds



Biosensors



GPCR Consortium

Michel Bouvier; *U de Montréal*

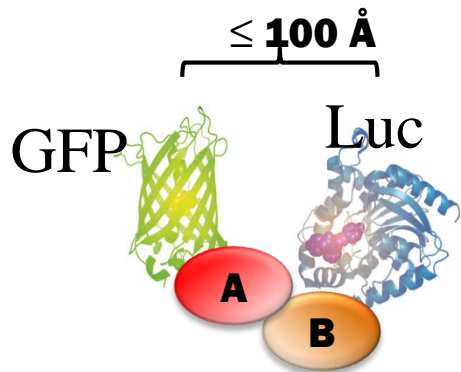
Terry Hébert; *McGill U.*

Stéphane Laporte; *McGill U.*

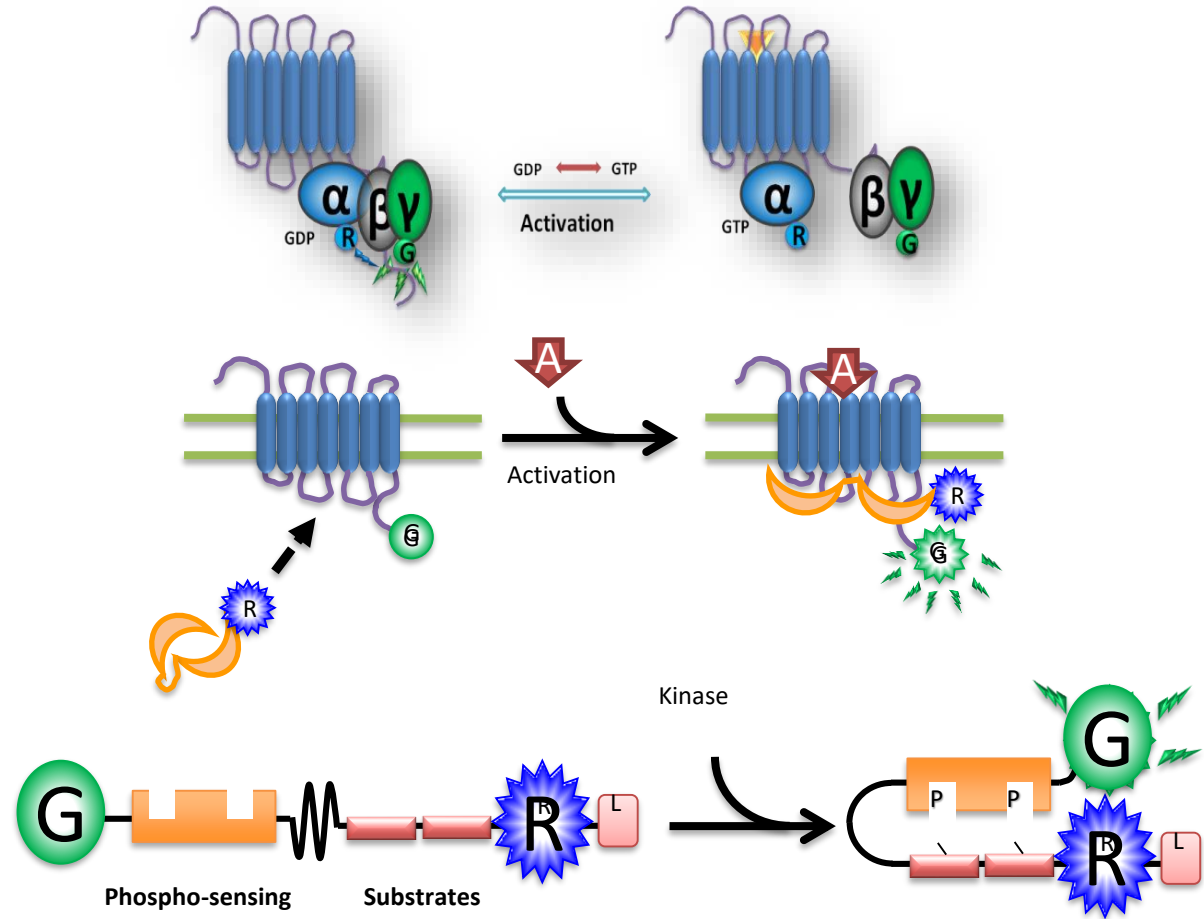
Richard Leduc; *U de Sherbrooke*

Christian Le Gouill; *U de Montréal*

Graciela Pineyro, *U de Montréal*



$$eBRET = 1/[1+(r/R0)^6]$$



More than 70 distinct sensors have been generated

Scientific Impacts

- Development and validation of more than 70 BRET-based biosensors probing GPCR activity
- Establishment and expansion of the concepts of functional selectivity and biased signaling
- Publication of more than 40 papers using the biosensors by team members
- Constant growth of publications using BRET sensors reaching 80/year in 2017
- Distribution of the biosensors to 115 different academic groups world-wide
- Validation of the link between biased signaling and functional outcomes for different GPCRs



Impacts for the Biopharmaceutical Sector

- CQDM Pharma Members:
 - ❖ In-licensing of the technology by Pfizer and Merck
 - ❖ Collaboration with Pfizer on a drug discovery project

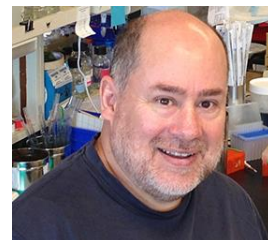
- Other Pharma Partners:
 - ❖ Establishment of drug discovery research projects with 3 additional pharmas
 - ❖ Licensing of the technology by Domain Therapeutics
 - Sublicensing of the technology to two large pharmaceutical companies

- Company creation:
 - ❖ Creation of a subsidiary of Domain Therapeutics in Montreal
 - Domain Therapeutics NA employs 8 HQP in Montreal
 - Executing collaborations/research contracts (more than 25 until now)

- Financial Returns:
 - ❖ Significant licensing fees returns to the inventors and institutions

- Training:
 - ❖ Training of more than 50 students, post-docs and research assistants

The GPCR Biosensor Consortium Team



Christian
Le Guill

Richard
Leduc

Terry
Hébert

Graciela
Pineyro

Stéphane
Laporte

Bouvier Lab
IRIC

Leduc Lab
IPS

Hébert Lab
Pharmacology

Pineyro Lab
Ste-Justine

Laporte Lab
MUHC

Université de Montréal

Université de Sherbrooke

McGill University

Université de Montréal

McGill University

Christian Le Guill
Victoria Lukashova
Mireille Hogue
Hélène Bonin
André Laperrière

Elie Simard
Jean-Michel Longpré

Dominic Devost
Nicolas Audet
Eugénie Goupil

Johanie Charbonneau
Karim Nagi
Besma Benredjmen

Étienne Khoury
Brandon Zimmerman
Yoon Namkung
Lama Yamani

Jonathan Gallion, Angela Wilkins **Olivier Lichtarge**; Baylor College

Outside collaborators:

Darren Cawkill, Mark Gosink, Stephen Jenkinson, Yong Ren,
Christopher Soms, **Anne Schmidt**; Pfizer