DSCTM

Conferenza di Dipartimento 2019

Premio YIA2019 - Chimica per la Salute e le Scienze della Vita
Gallo Carmela - ICB

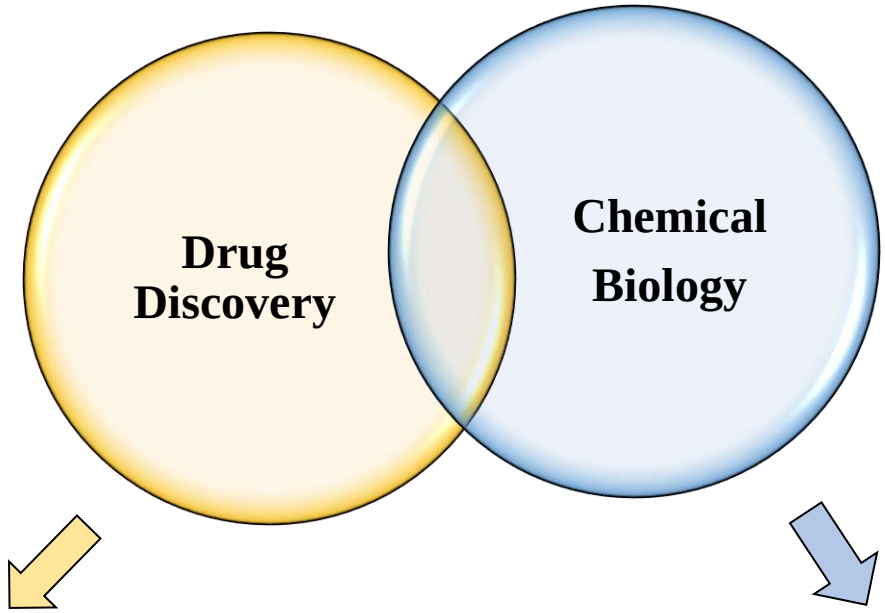
# Characterization, biosynthesis and functional biochemistry of lipid mediators from marine organisms

*Bio-Organic Chemistry Unit*

*CNR- Istituto di Chimica Biomolecolare (ICB) - Via Campi Flegrei 34, 80078 Pozzuoli, NA, Italy.*

*e-mail: carmen.gallo@icb.cnr.it*

# Characterization, biosynthesis and functional biochemistry of lipid mediators from marine organisms

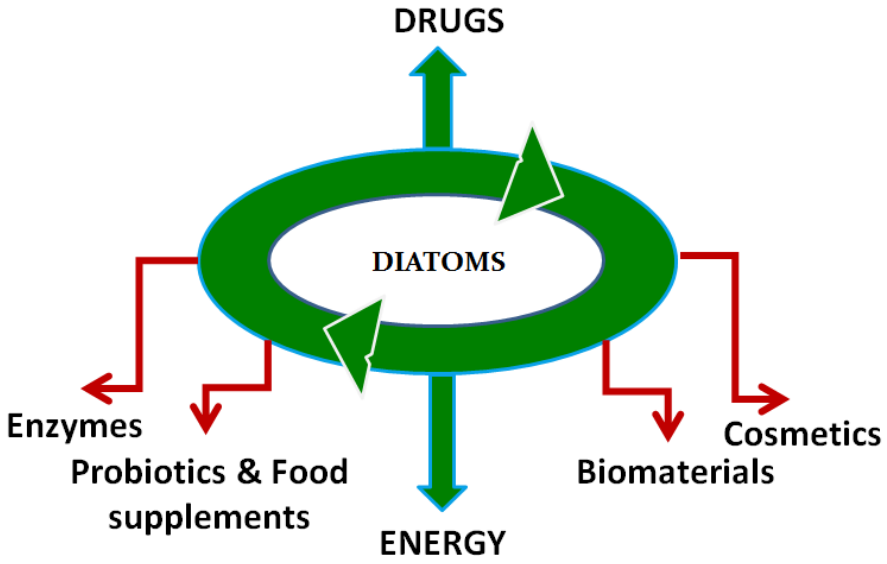


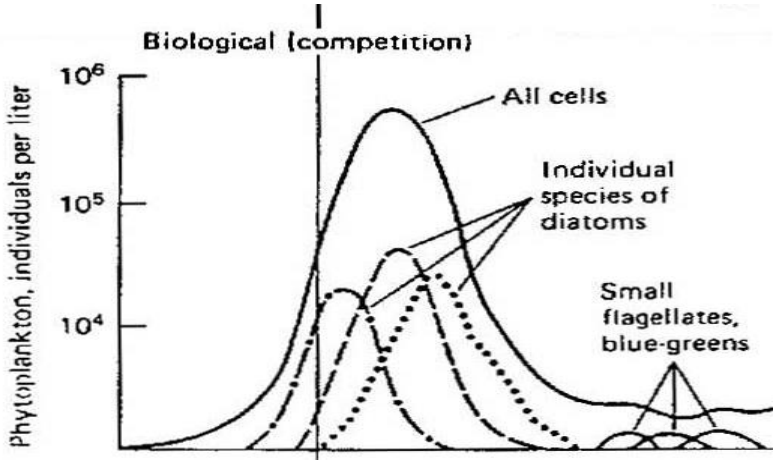

Characterization of natural compounds isolated from marine organisms and synthetic derivatives with immunomodulatory and antitumoral properties

Isolation and characterization of natural molecules with an eco-physiological and biochemical role in the metabolism of unicellular organisms

# Diatoms

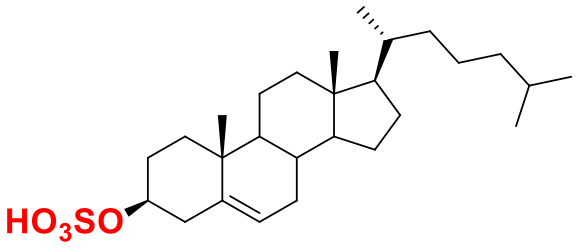
one of the most ecologically relevant group of organisms on Earth



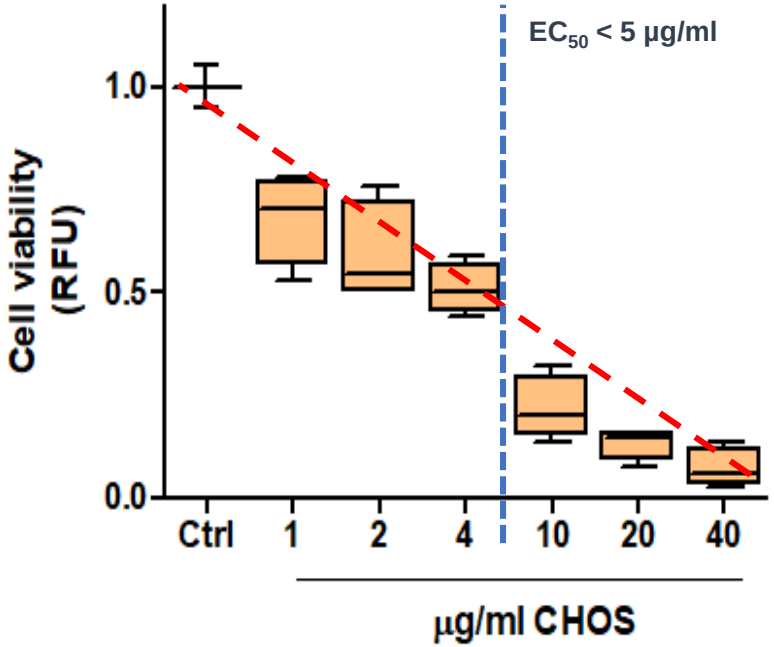




Satellite image of algal bloom, off Southwest England.
Image: NASA

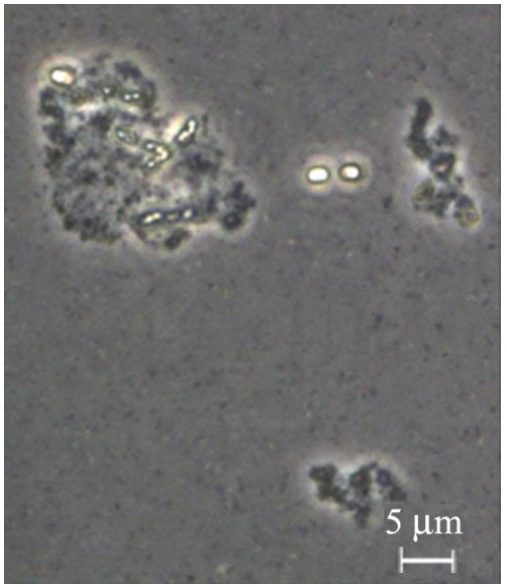
# Characterization of autoinhibitory compounds in Microalgae: Sterol sulfates




**Cholesterol sulfate**

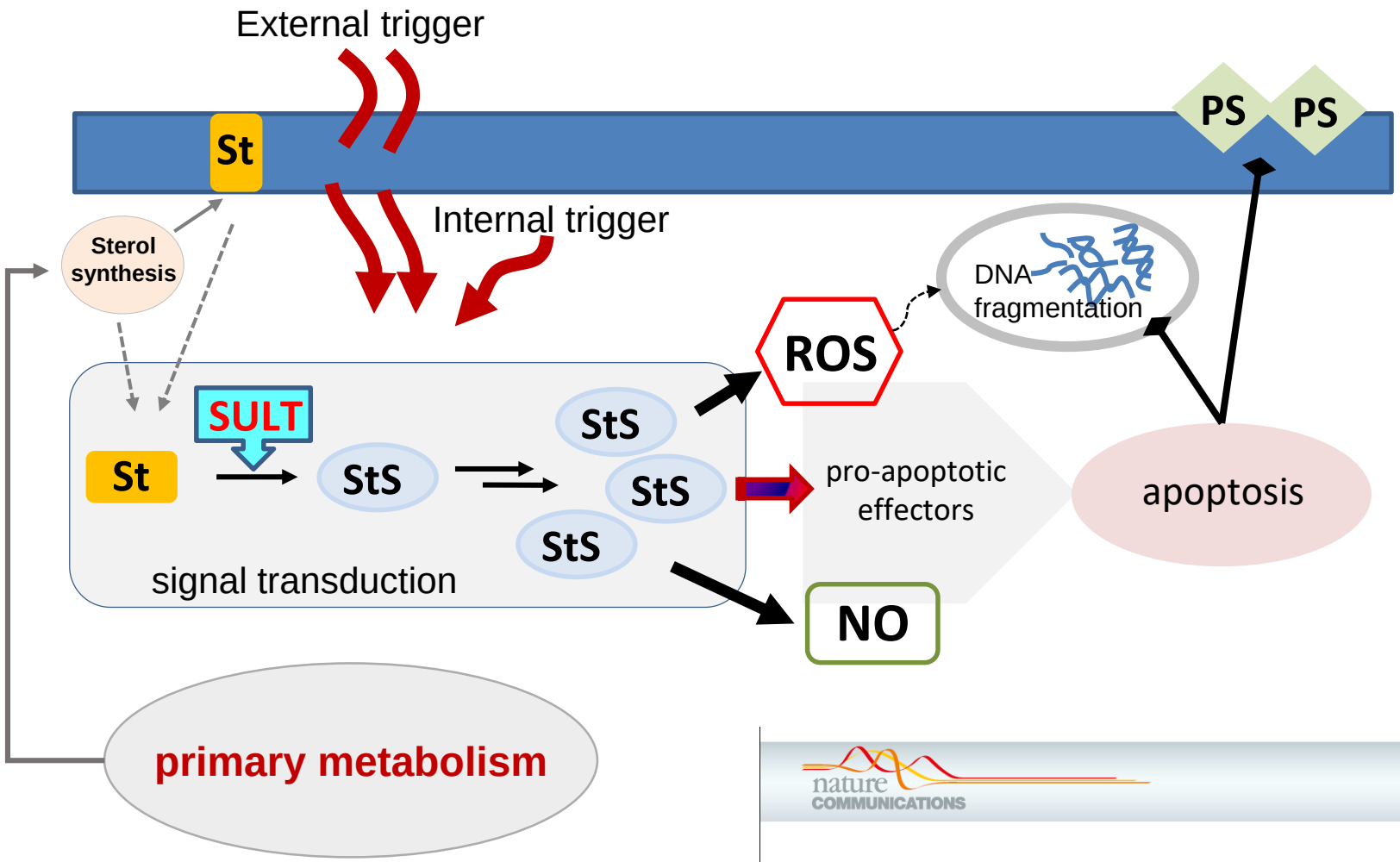



**Senescent Culture**




*Gallo et al., Nature Comm. 2017*

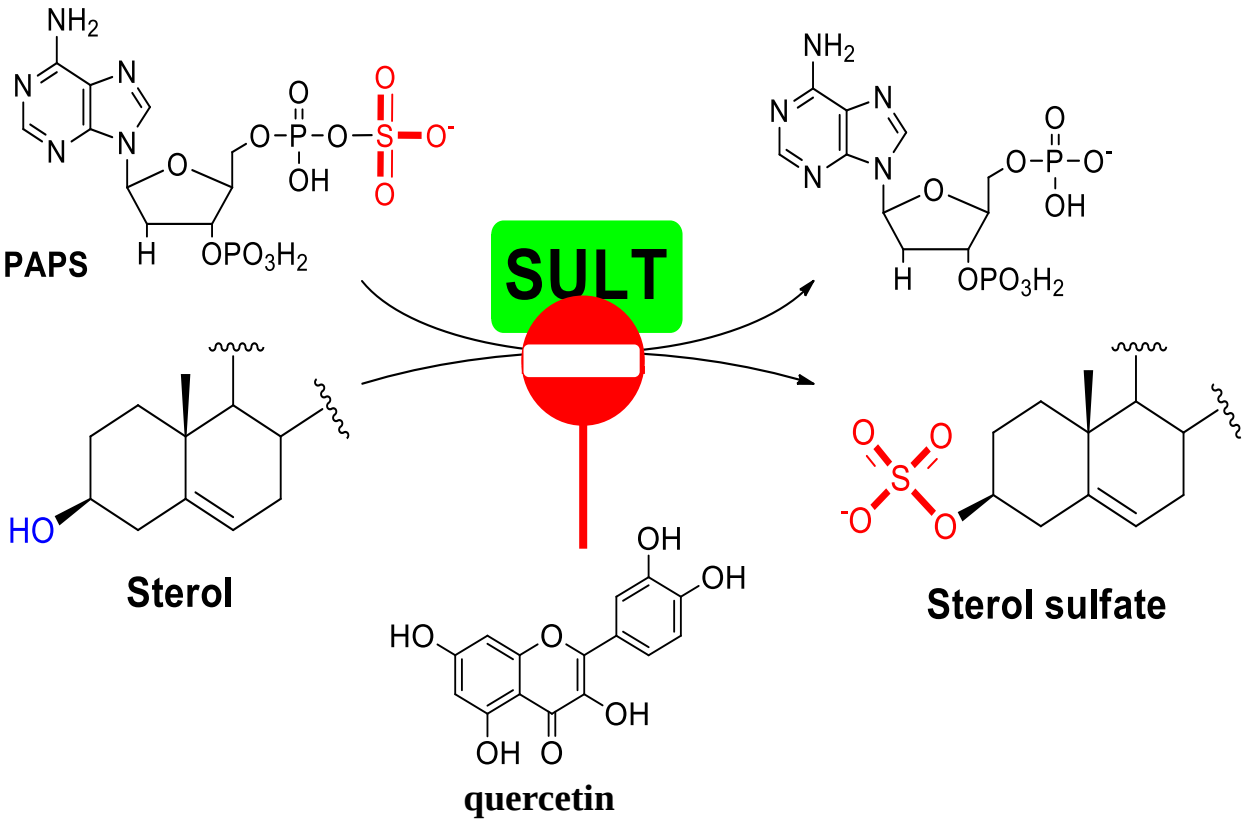
# Signaling transduction by sterol sulfates in *S. marinoi*





*Gallo et al., Nature Comm. 2017*

# SULT inhibition

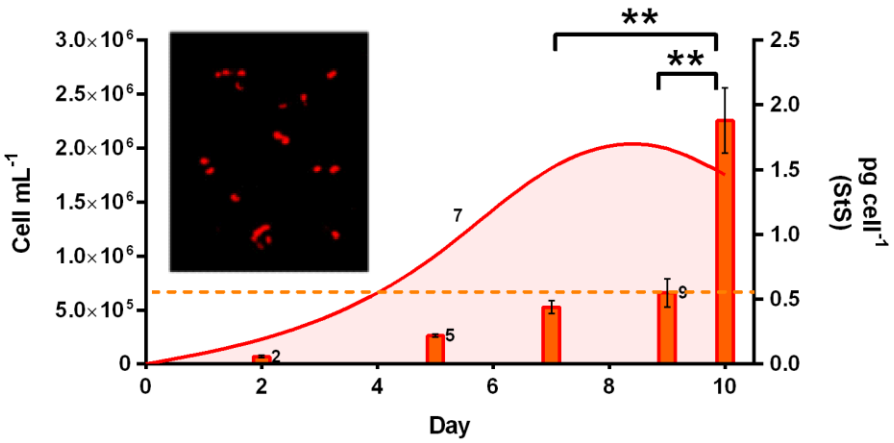



(SULT1B inhibitor)

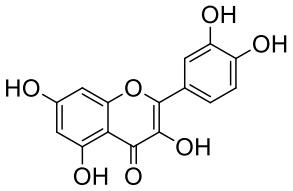
*Gallo et al., Nature Comm. 2017*

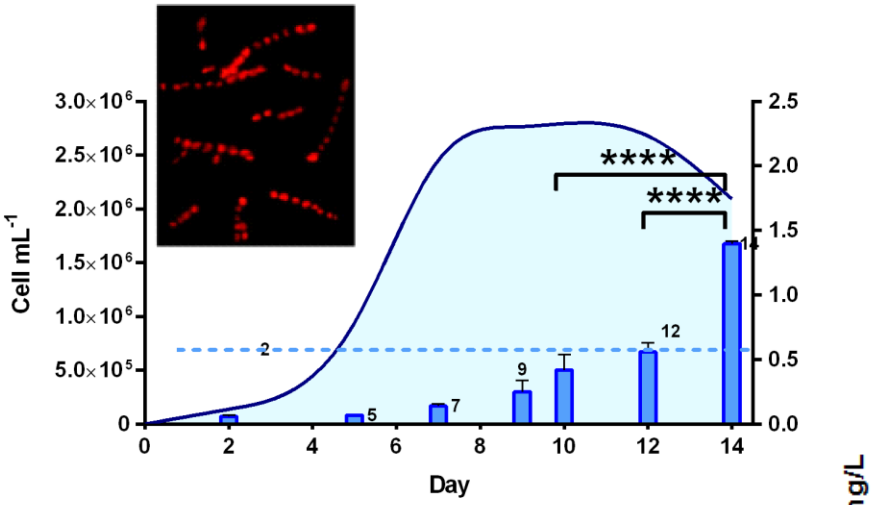
# Sterol sulfates biochemical inhibition

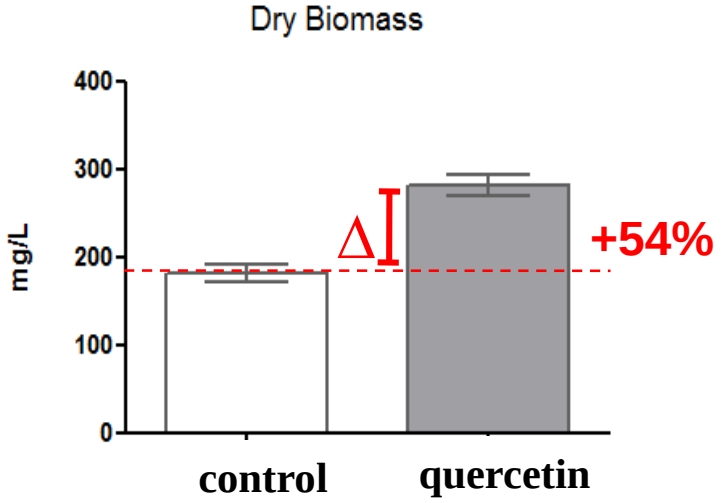
## Control




## Quercetin



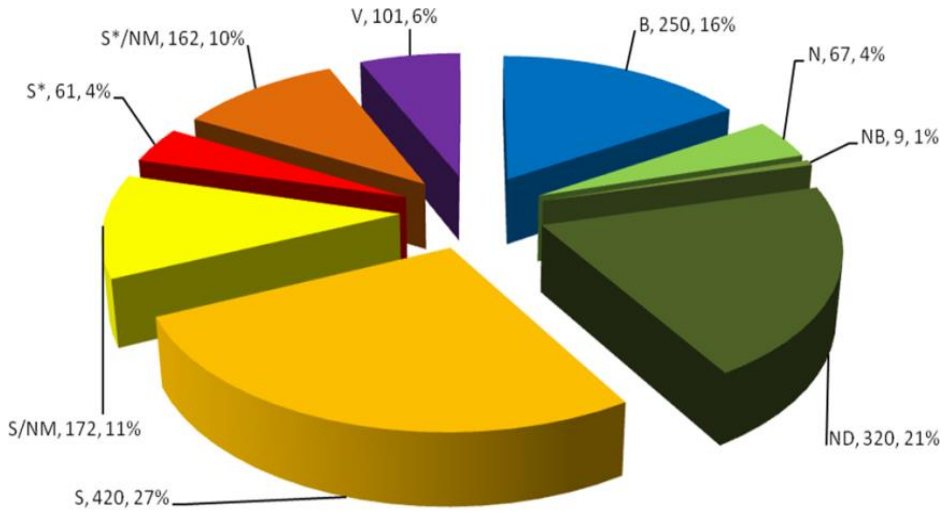




*Gallo et al., Nature Comm. 2017*

# Natural Products:
# a continuing source of novel drug leads

## All new approved drugs 1981-2014



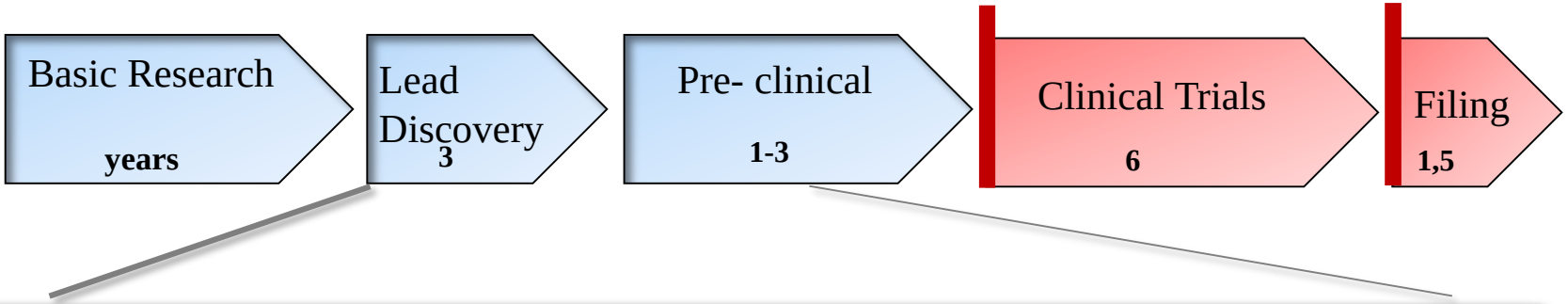

| | |
|---|---|
| B | Biological macromolecule |
| N | Natural product |
| NB | Botanical drug (defined mixture) |
| ND | Natural product derivative |
| S*/NM | Mimic of natural product |
| S* | Synthetic drug (NP pharmacophore) |
| S/NM | Mimic of natural product |
| S | Synthetic drug |
| V | Vaccine |

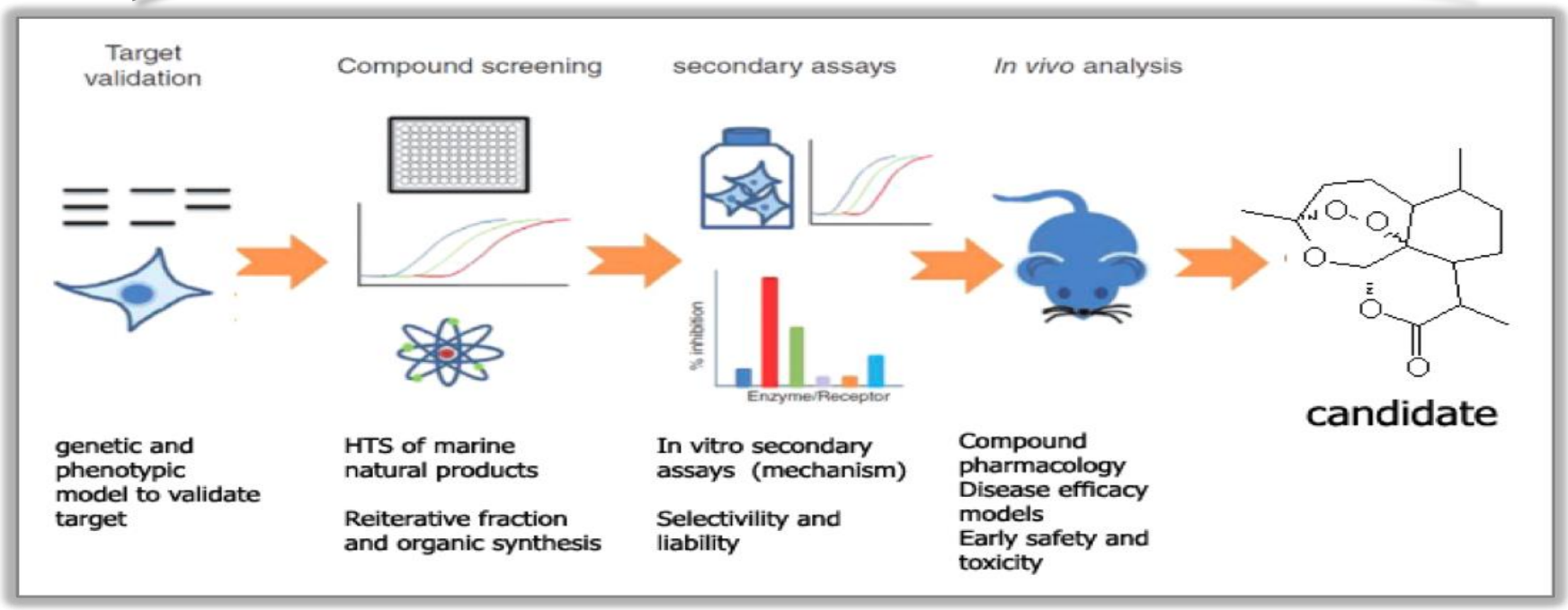
*Newman,D. J. Cragg, G. J. Nat. Prod. 2016*

# Drug discovery process

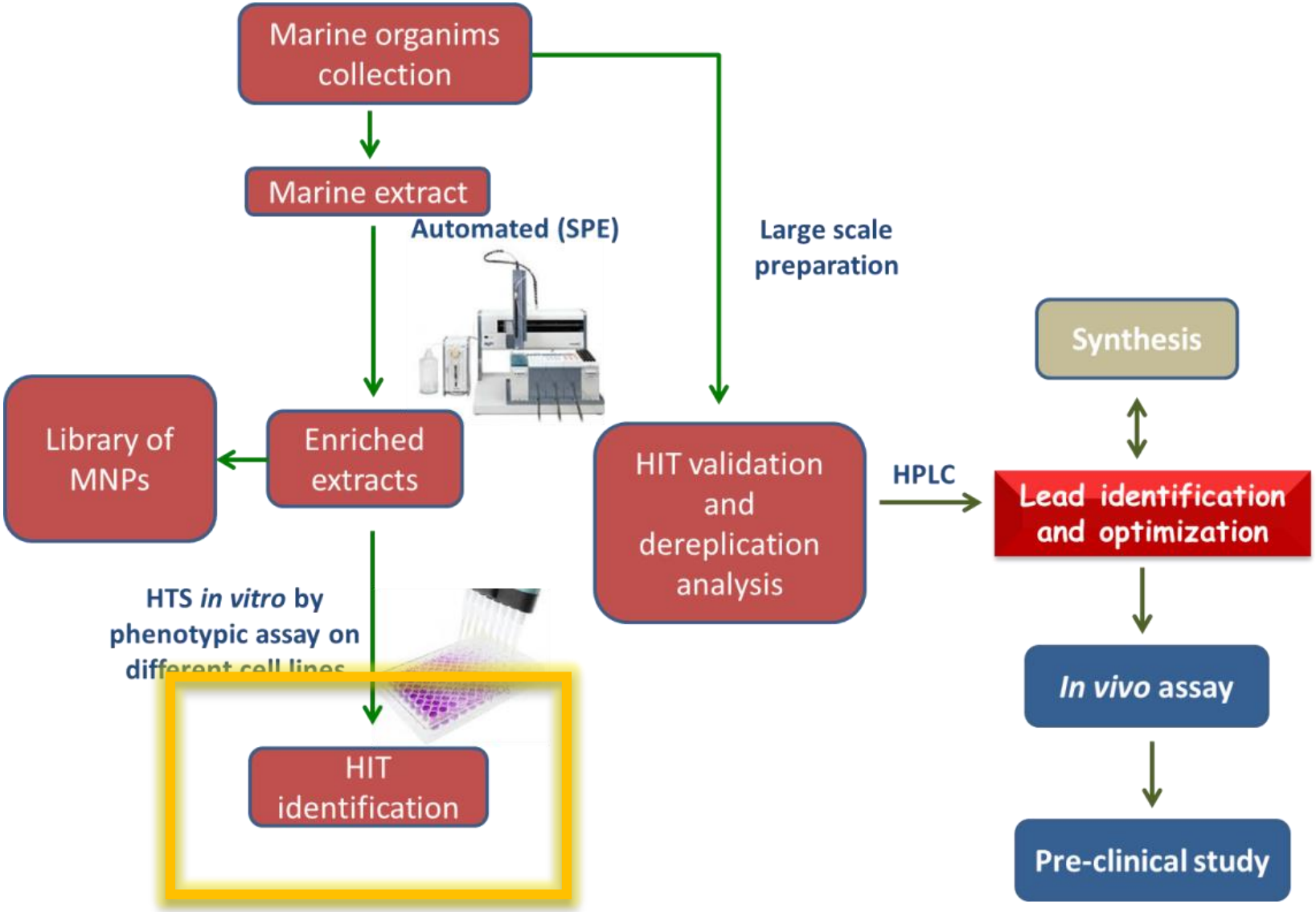
Investigational New Drug (IND)

New Drug Application (NDA)



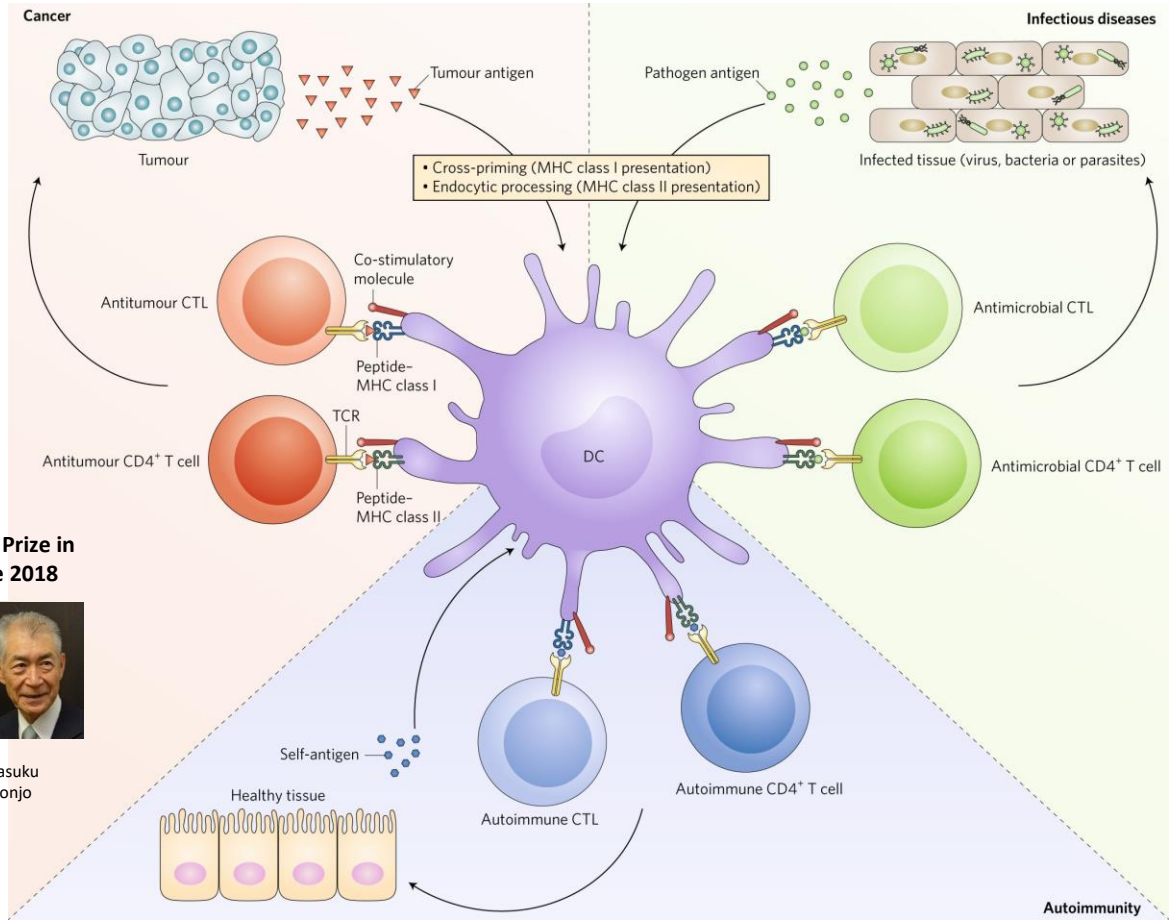




**Identify new natural compounds from marine organisms with antineoplastic and immunomodulant properties**

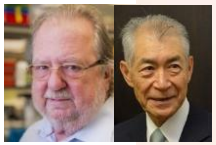

Marine organims collection
Marine extract
Automated (SPE)
Large scale preparation
Library of MNPs
Enriched extracts
HIT validation and dereplication analysis
HPLC
Synthesis
Lead identification and optimization
HTS *in vitro* by phenotypic assay on
HIT identification
*In vivo* assay
Pre-clinical study

# Cancer Immunology and Immunotherapy

## Role of Professional Antigen Presenting Cell




**The Nobel Prize in Medicine 2018**



James P. Allison

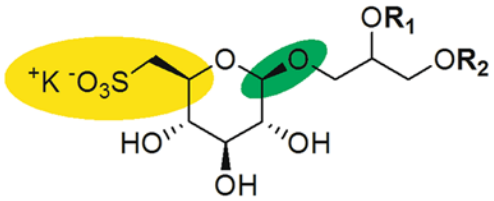
Tasuku Honjo

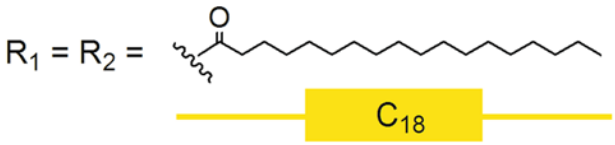
**Substances activating DC: potential <u>adjuvants and/or vaccines!</u>**

# β-Sulfoquinovosyl-diacylglycerol (β-SQDG)
# SULFAVANT- A (SULF-A)

IT1417828 (04/09/2015) - EP20140741377 (20/04/2016)

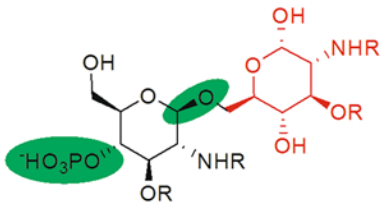
CN105307680A, US20160151483, WO2014199297A1

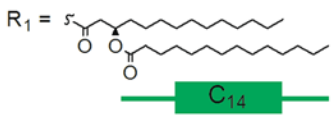



## High immunomodulant activity

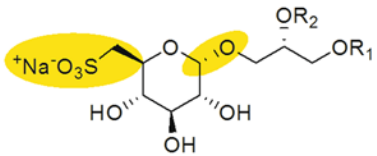
3-*O*-desacyl-4'-monophosphoryl lipid A
**MPL®**

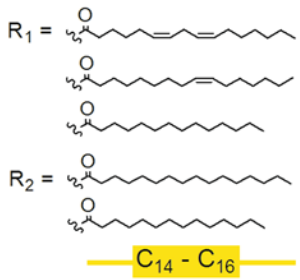



(First new Food and Drug Administration-approved adjuvant in over 70 years)

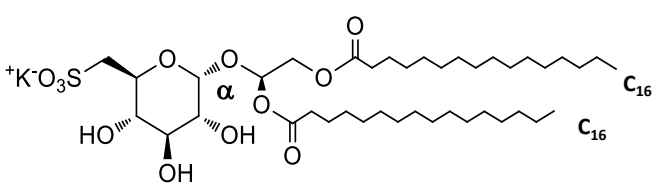
a-Sulfoquinovosyl diacylglycerols
(α-SQDG) isolated from diatoms



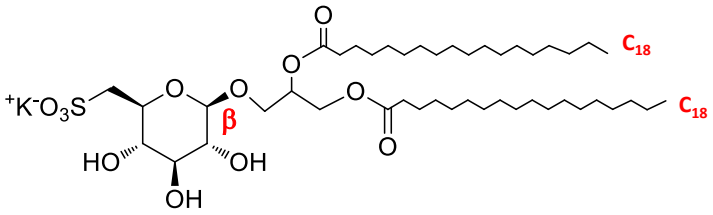




*Thalssiosira weissflogii*

# Improvement of Immune Activity: SULF-A

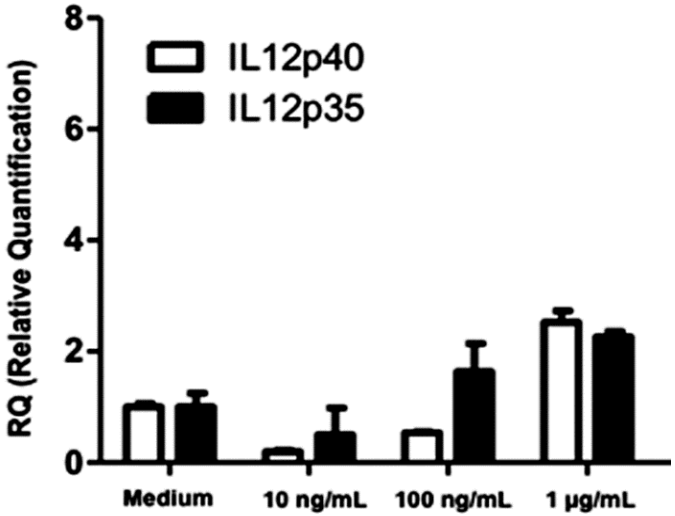



Synthetic α-SQDG

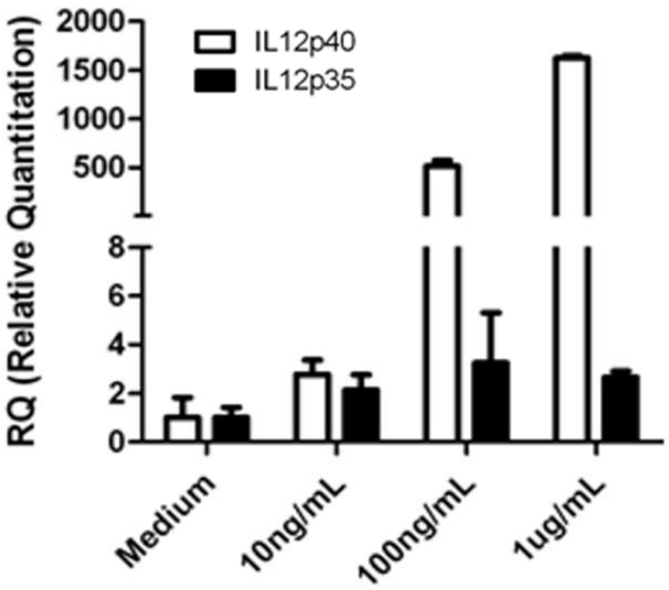



Sulfavant A (β-SQDG)

**24h**



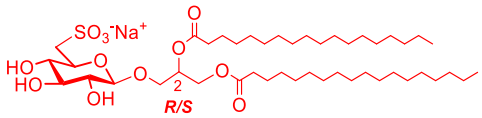

**24h**




**No cytotoxicity up to 30 mg/ml**

*Manzo et al., Scientific Reports, 2017*

# Next step: improvement of the sulfolipid scaffold synthesis and preparation of two epimers

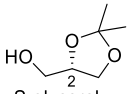


**Sulfavant A**

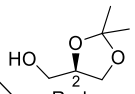
**(mixture of epimers at C2)**

**DC maturation at 10µM**

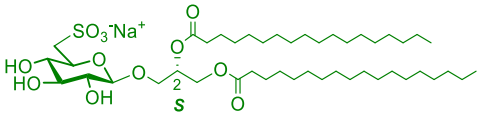
Glucose



S-glycerol acetonide



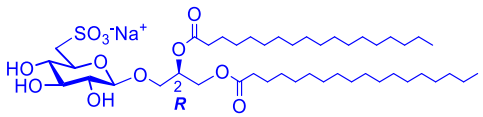
R-glycerol acetonide



**Sulfavant S**

**(pure *S*-epimer at C2)**

**DC maturation at 10nM**

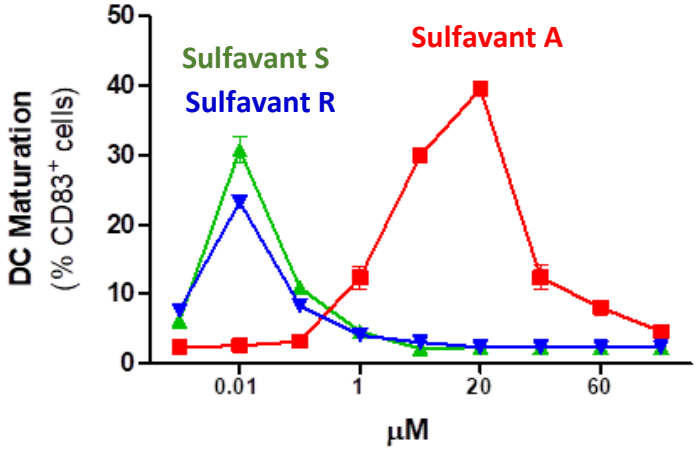


**Sulfavant R**

**(pure *R*-epimer at C2)**

**DC maturation at 10nM**

**Pure epimers were more potent than mixture**

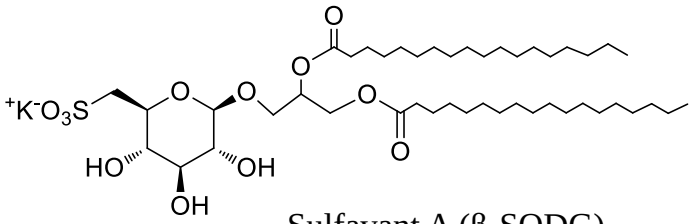



In progress: **Correlation of Immunomodulant Activity with Supramolecular Aggregation**

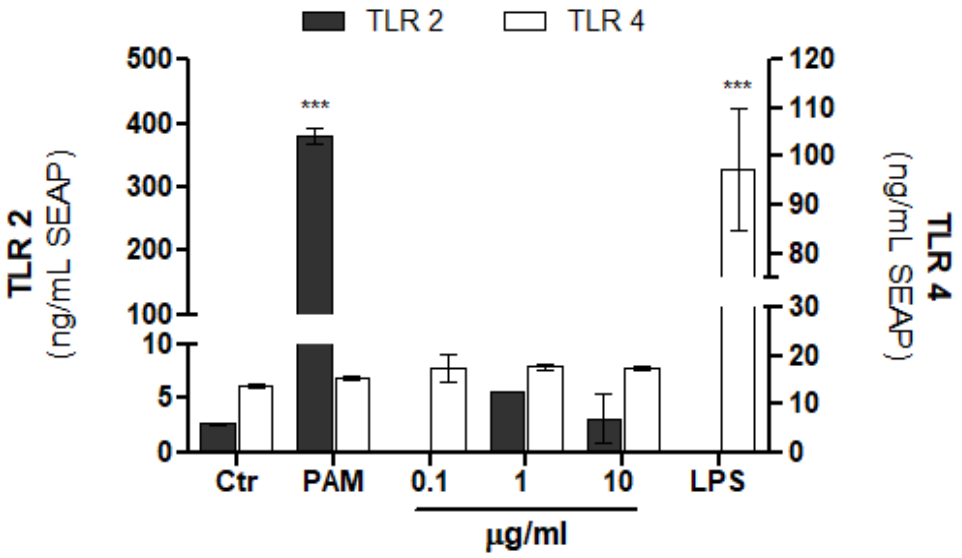
*Manzo et al ACS Omega, 2019, 4 (4), 7807-7814*

# SULF-A: a novel family of immunomodulators?

SULF-A activity is independent of Toll-Like Receptor 2 and 4



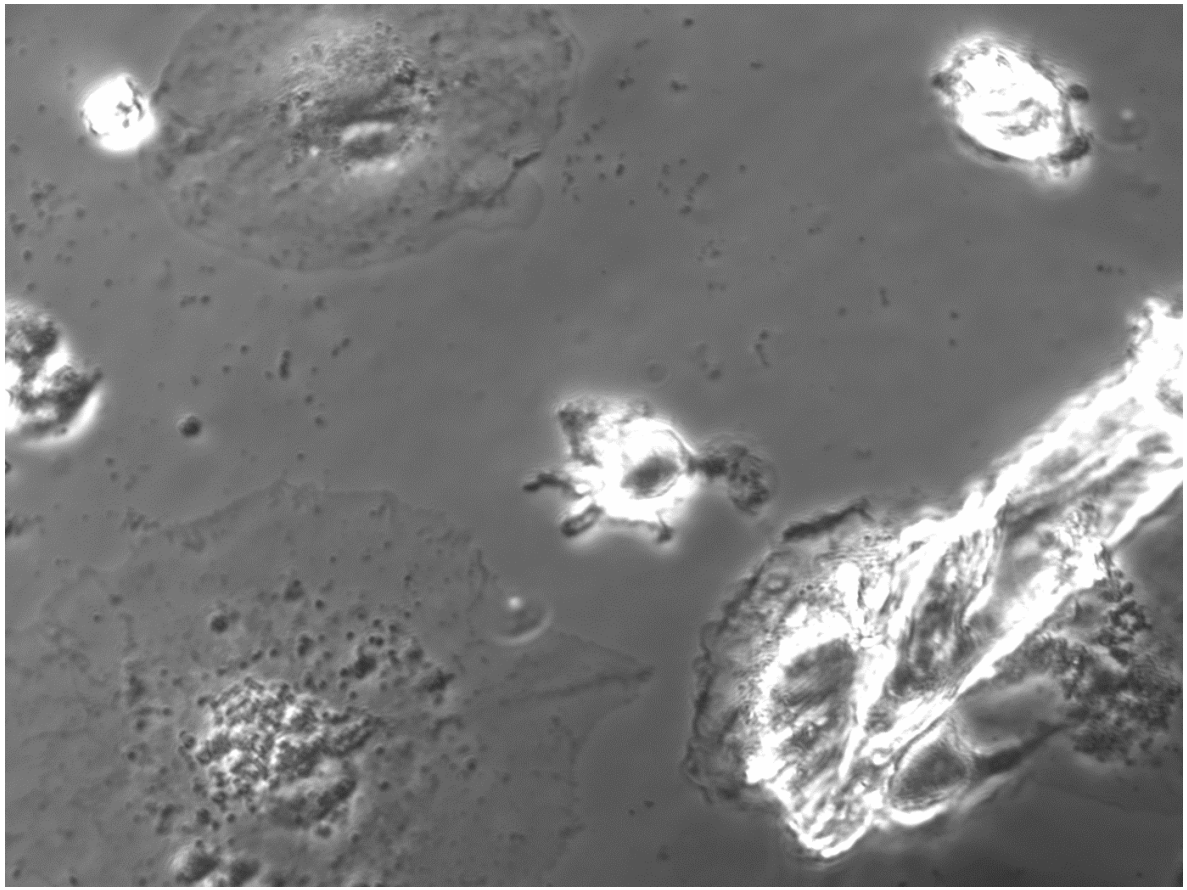

Sulfavant A (β-SQDG)




*Manzo et al., Scientific Reports, 2017*

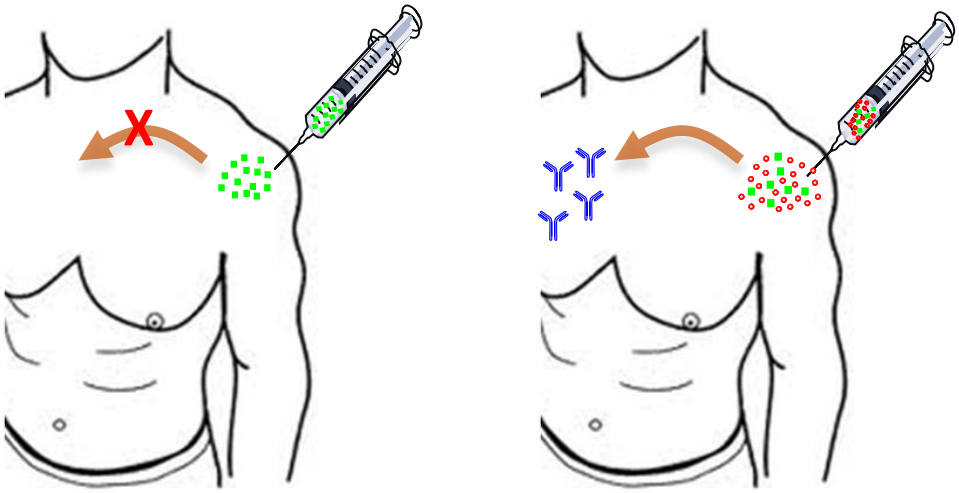
# SULF-A: beyond the Dendritic cells

## Activation of Microglia cell by SULF -A

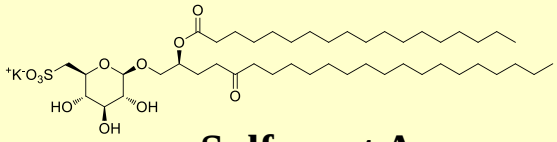


**Time lapse microscopy experiment – 24 h- 10 ug SULF-A**

# IMMUNOMODULATOR & VACCINE ADJUVANT




= immune response
= recombinant protein
= adjuvant



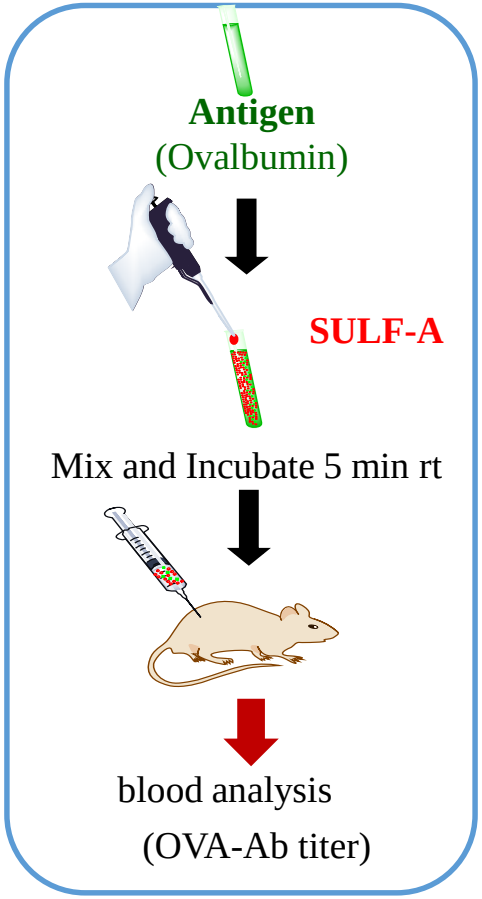
**Sulfavant A**

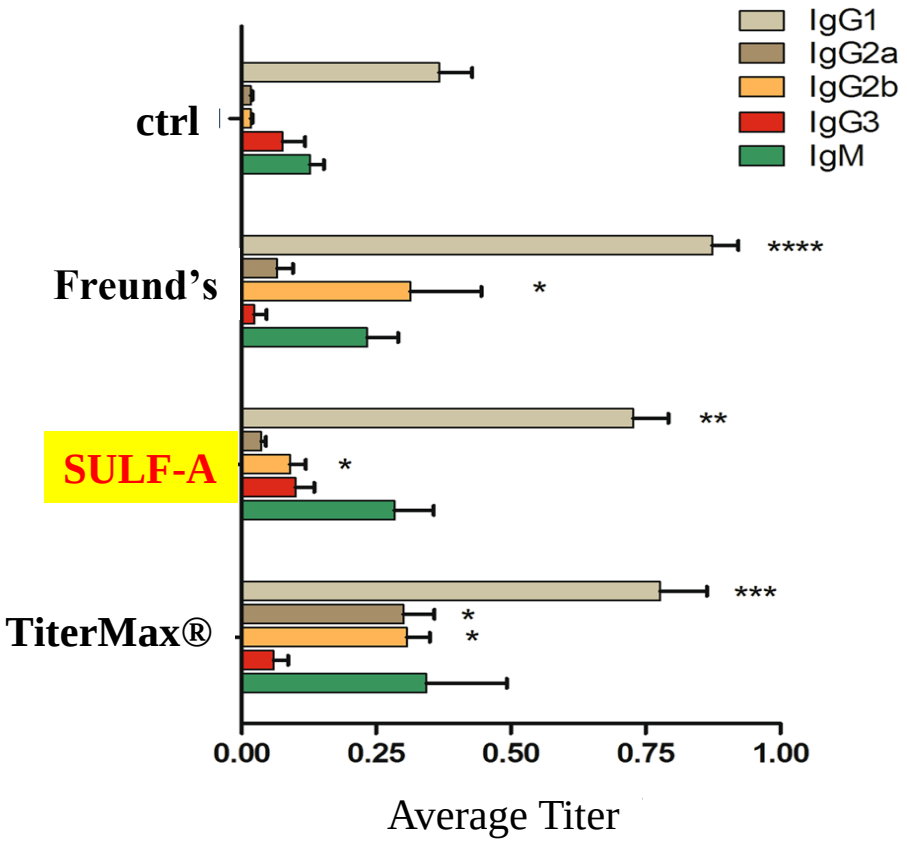
marine algae-derived molecule

- ✓Novel class of molecular adjuvant
- ✓Patent n. (EP3007725 B1)
  (WO 2014/199297; Priority: MI0001417828)
- ✓Synthetic product
- ✓Non-toxic
- ✓Novel mechanism of action
- ✓Stable formulations

# SULF-A as *in vivo* adjuvant

## Immunization test



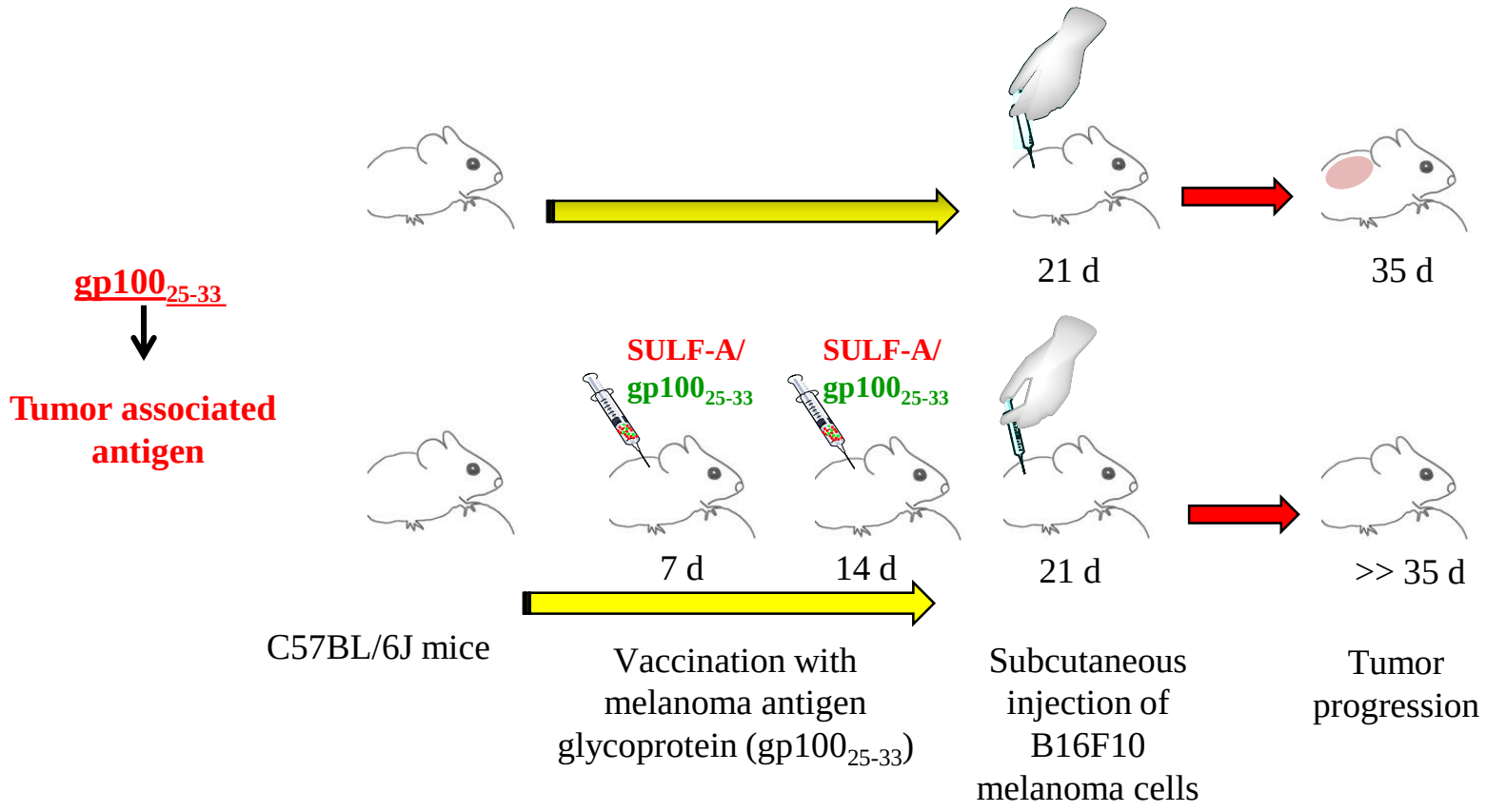




- ✓ **National patent IT1417828 (granted on 04/09/2015)**
- ✓ **International application (PCT/IB2014/062098)**

*Manzo et al., Scientific Reports, 2017*

# SULF-A as *in vivo* adjuvant → Cancer immunotherapy

## β-SQDG tested in an experimental model of cancer vaccine against a murine B16F10 melanoma cell line

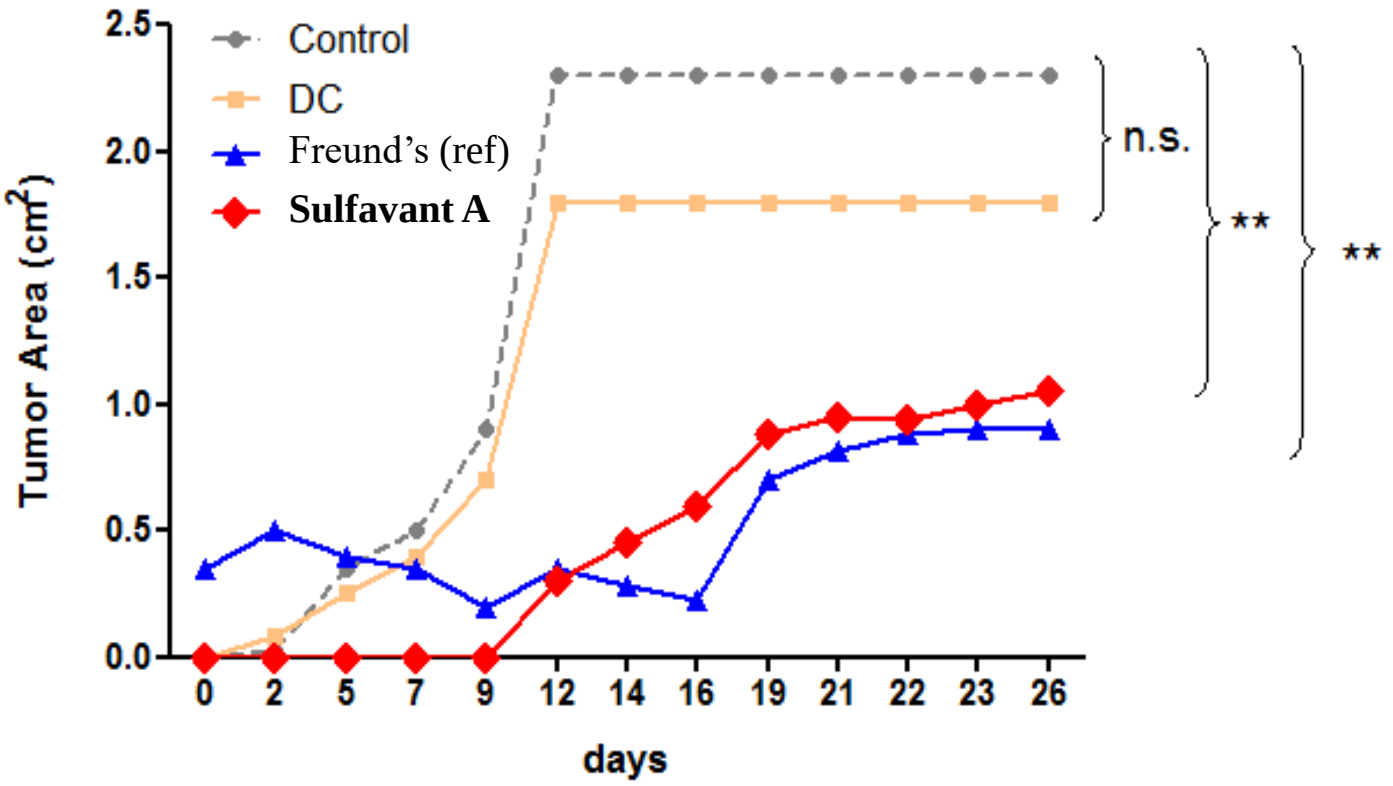



In collaboration with prof. Gilberto Filaci, Internal Medicine and Clinical Immunology Univeristy of Genova

*Manzo et al., Scientific Reports, 2017*

# SULF-A (β-SQDG) as *in vivo* adjuvant

**β-SQDG tested in an experimental model of cancer vaccine against a murine B16F10 melanoma cell line**




*Manzo et al., Scientific Reports, 2017*

**A**ntitumor **D**rugs and **V**acc**i**nes from the **SE**a

POR FESR 2014-2020 - ASSE I - AVVISO PUBBLICO: MANIFESTAZIONE DI INTERESSE PER LA REALIZZAZIONE DI TECHNOLOGY PLATFORM NELL' AMBITO DELLA LOTTA ALLE PATOLOGIE ONCOLOGICHE - DD DG 10 93 N. 355/2017 E SS.MM.E II.: RIAPERTURA DEI TERMINI DI PRESENTAZIONE DELLE DOMANDE, MODIFICHE E INTEGRAZIONI ALL'AVVISO, PUBBLICAZIONE DEL VADEMECUM E DELLA MODULISTICA.

Budget: **16.320.680 Euros**

Start: 1st January 2019 End: 31 December 2021

Leading : CNR-DSCTM - General Coordinator: Dr. Angelo Fontana (CNR-ICB)

# Progetto **ADViSE**

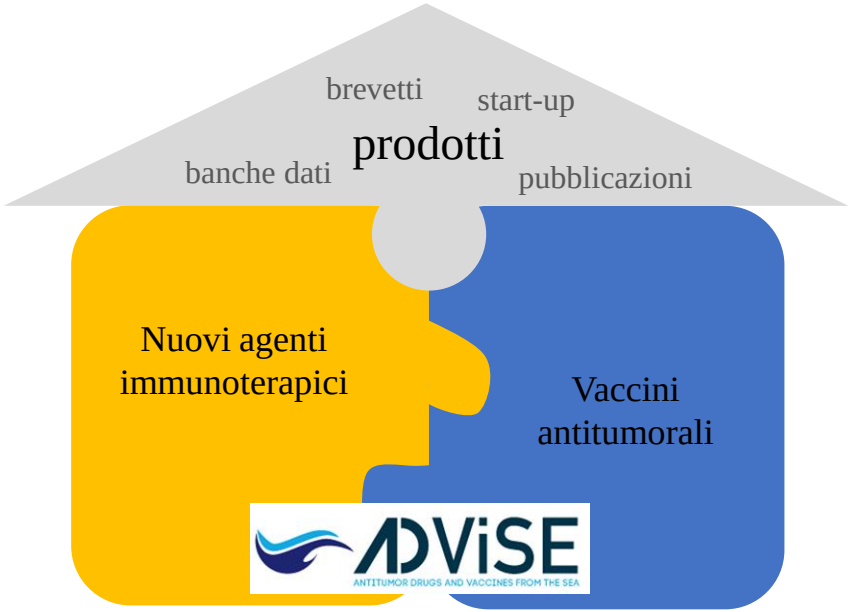
**A**ntitumor **D**rugs and **V**accines from the **SE**a
Oncology Platform - D.D. 403 on 12/11/2018 and 422 of 16/11/2018

**Objectives**:

1) Entrance in Phase 1 Clinical Trial for Sulfavant as vaccine adjuvant

2) Preclinical development of recombinant vaccines for:
   - Melanoma
   - Multiple myeloma
   - Lung Cancer

3) Drug Discovery Platform based on Marine Natural Products (DD-MNP)



Bio-Organic Chemistry Unit (BOCU)

## Acknowledgements


Dr Angelo Fontana
Dr. Giuliana d'Ippolito
Dr. Jenny Nuzzo
Dr. Emiliano Manzo
Dr. Laura Fioretto
Dr. Giusi Barra
Dr. Marisa Saponaro
Dr. Marcello Ziaco
Mr. Lucio Caso

Prof. Raffaele De Palma, SUN

Prof. Gilberto Filaci, CEBR UniGE

Prof. Marco Colonna, WUSTL
Prof. Marina Cella, WUSTL