

Cycle : Pour le Développement des Sciences et de l'Innovation (PDSI) au service des Transitions

Jeudi 16 Juin 2022 à l'Hôtel de l'Industrie



L'olfaction, une fonction vitale ?



Pr Francis Galibert, Pharmacien, docteur ès sciences physiques, membre de l'Académie nationale de médecine, membre de l'EMBO (Organisation européenne de biologie moléculaire)



Calice Becker, Parfumeur, Directrice de l'Ecole de parfumerie Givaudan

Modération par

Pr Patrice Debré, Vice-Président de l'AFAS



Pr Francis Galibert

Pharmacien, docteur ès sciences physiques, membre de l'Académie nationale de médecine, membre de l'EMBO (Organisation européenne de biologie moléculaire)



Olfaction, une fonction vitale

Francis Galibert

Professeur émérite

Membre de l'Académie de Médecine

AFAS 16 juin 2023

Recherche de nourriture

Détection des dangers, des prédateurs

Recherche de partenaires sexuels

.....

PLAN

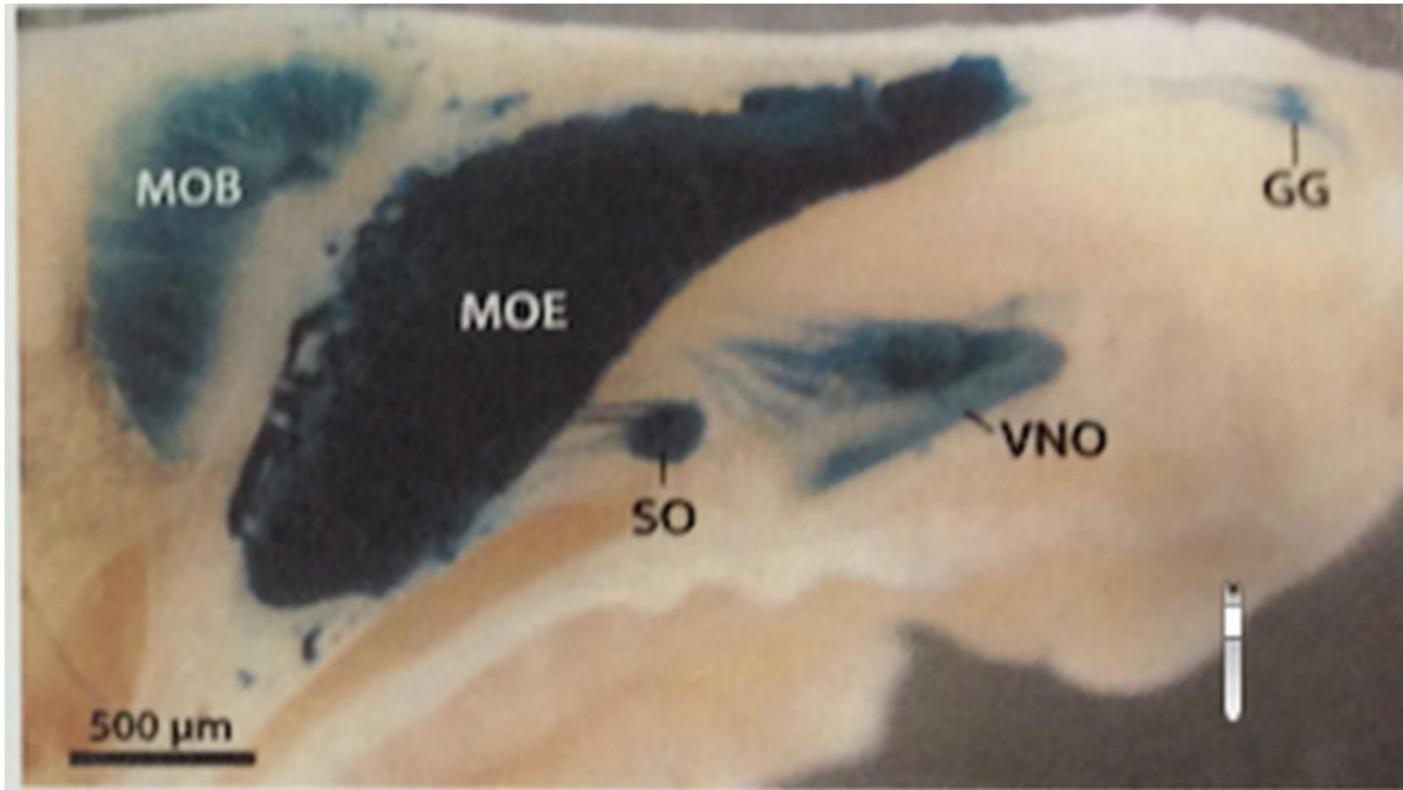
Quelques notions d'anatomie

Biologie de l' olfaction

Quelques données expérimentales

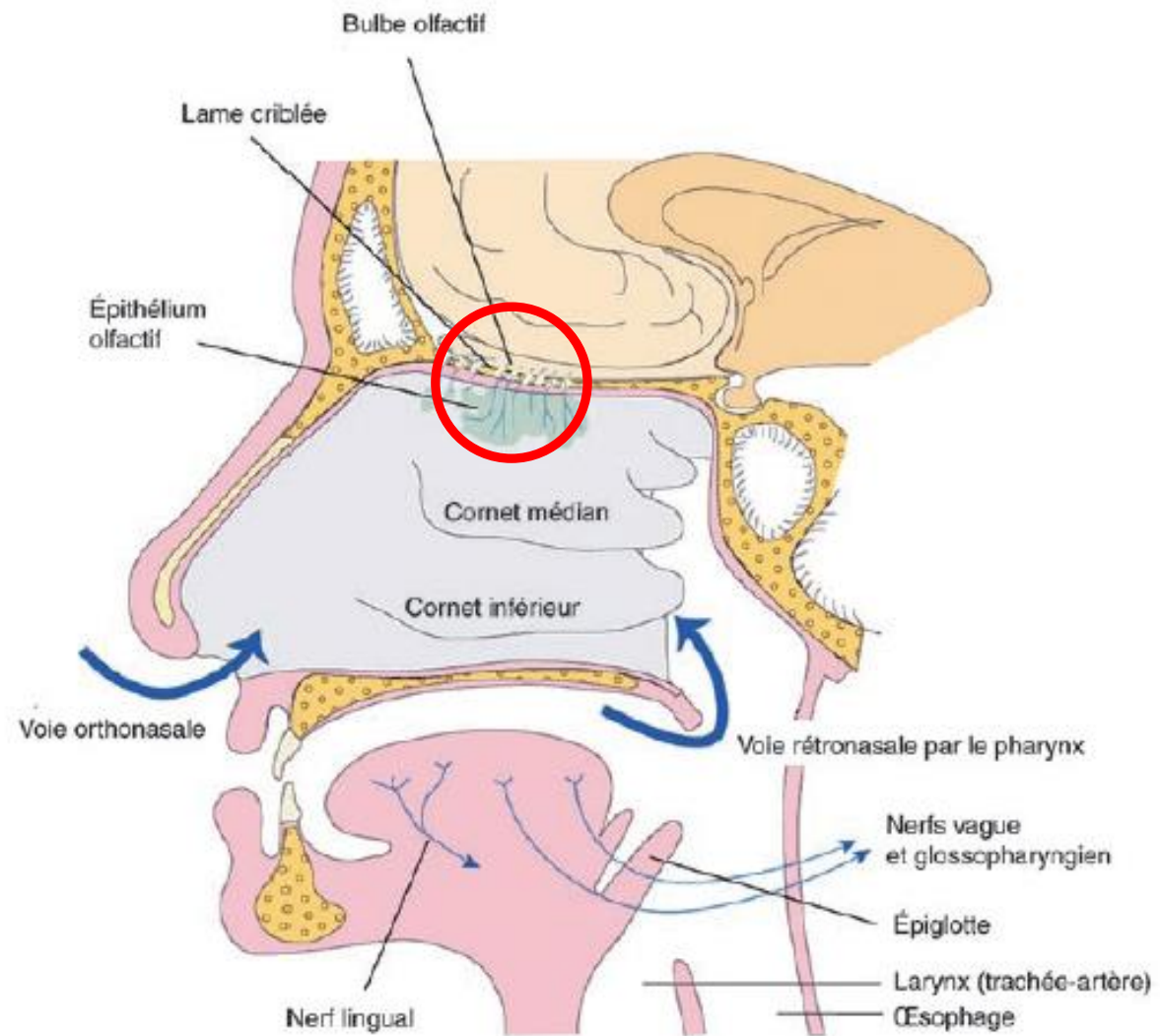
Conclusion

La détection et l'identification des odeurs est un phénomène complexe qui implique des structures périphériques (le nez) et centrales (bulbe olfactif, cerveau)



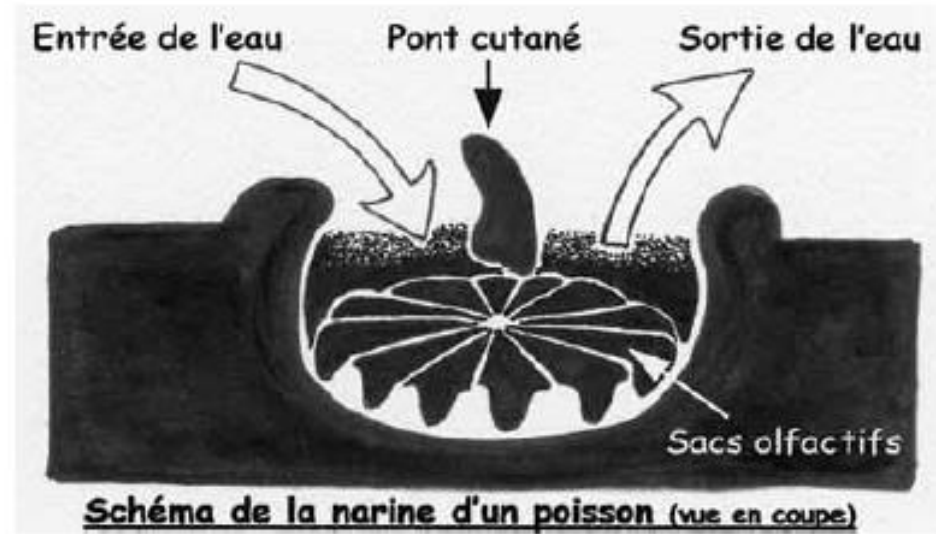
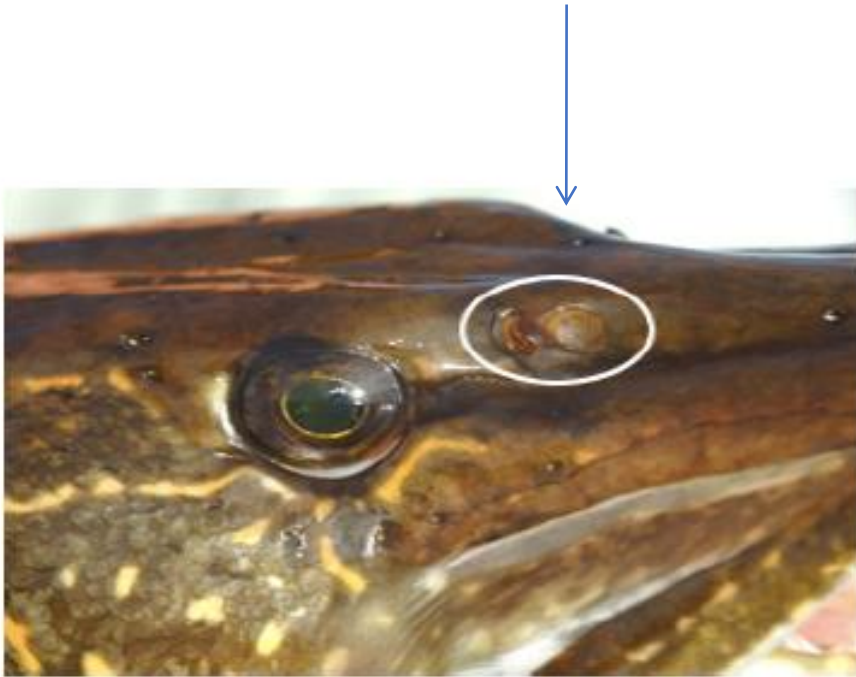
- L'organe principal ou MOE
- L'organe vomerobasal ou VNO
- organe de Masera ou SO
- ganglions Grueneberg GG

From Munger et al. 2009

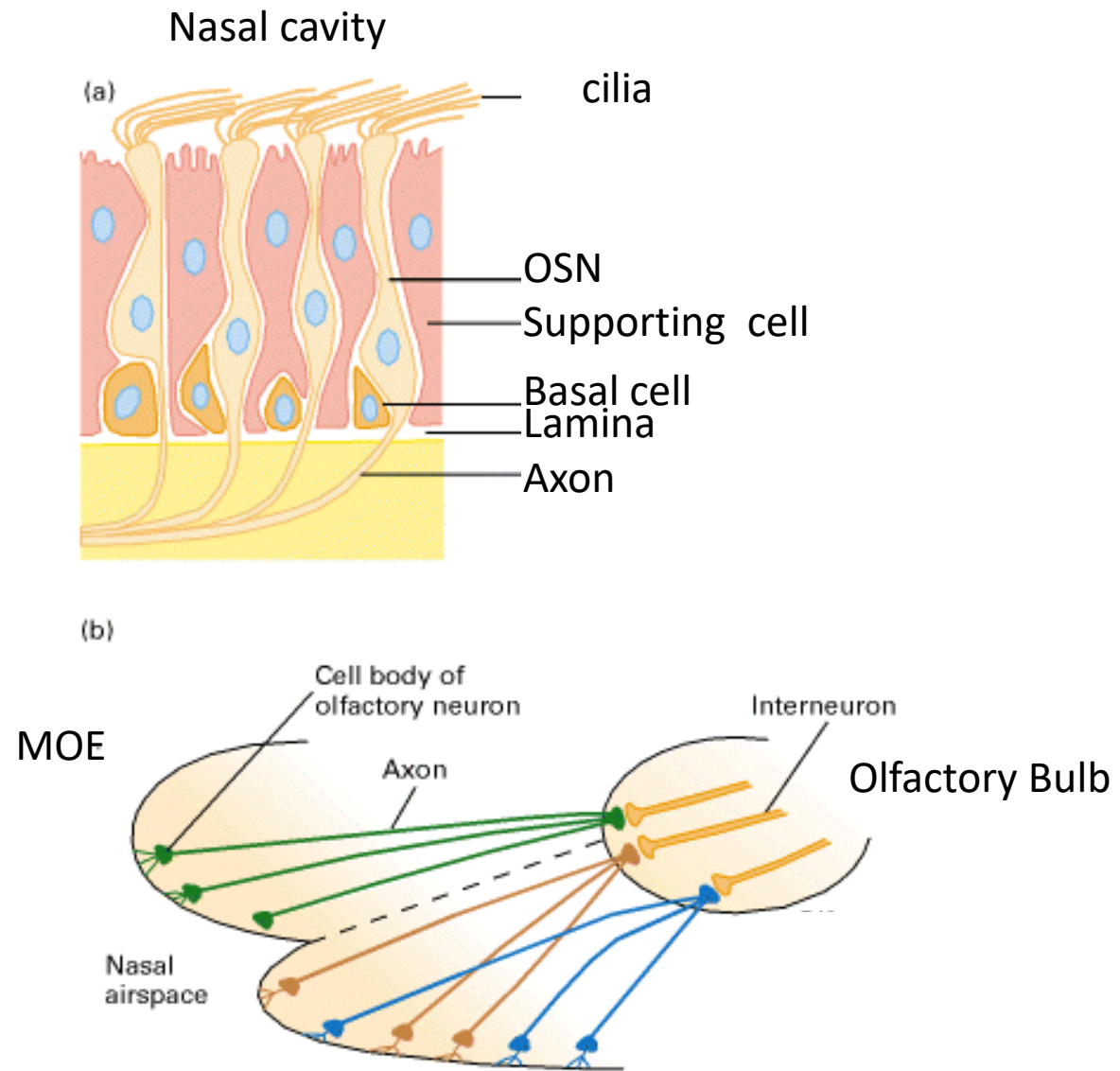


The two airflow routes

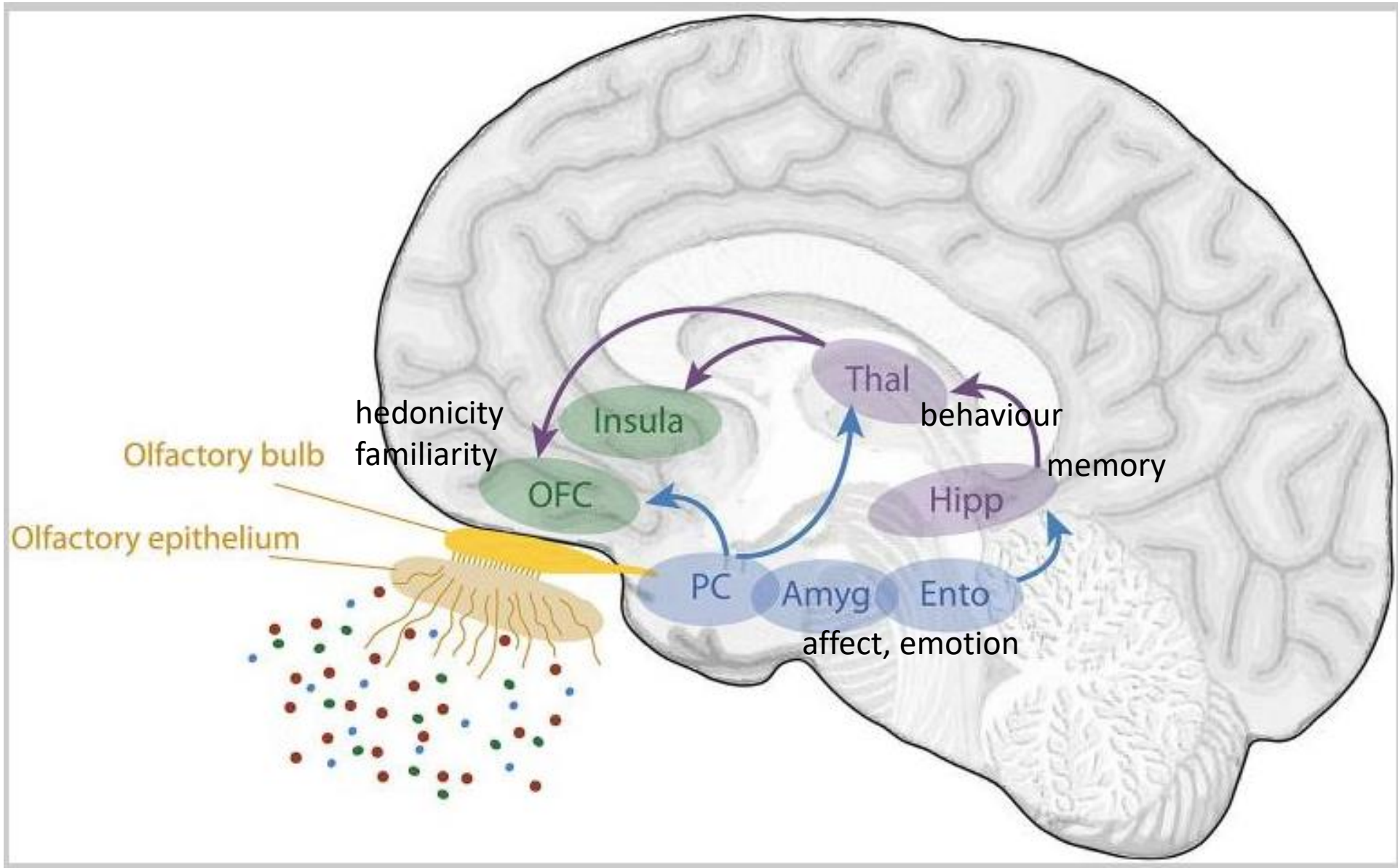
nostril



From Azzouzi N (2014)



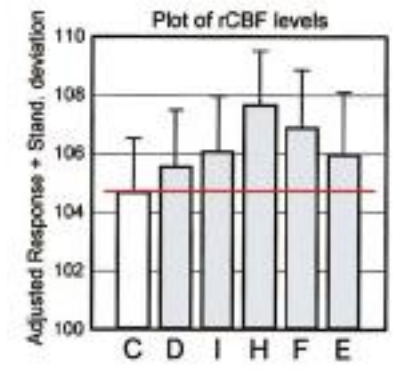
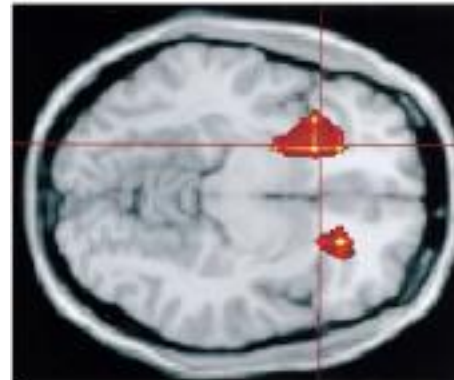
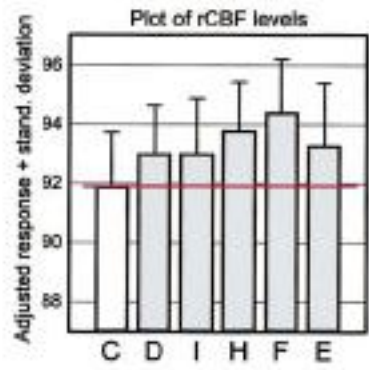
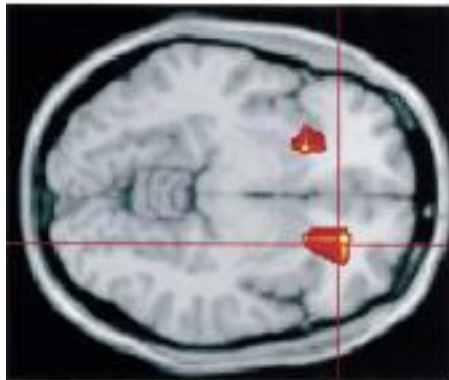
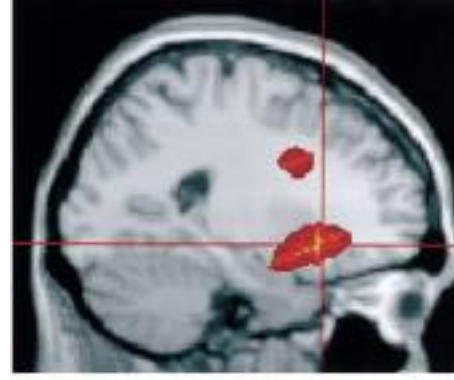
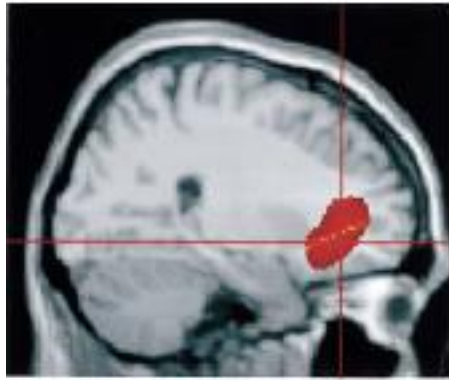
Axons from OSN expressing the same OR converge to the same nodule



From Anne-Lise Saive et al. 2014

Sagittal

Transversal



Horizontal section

Familiarity test

Hedonicity test

from Royet et al. 2001, NeuroImage

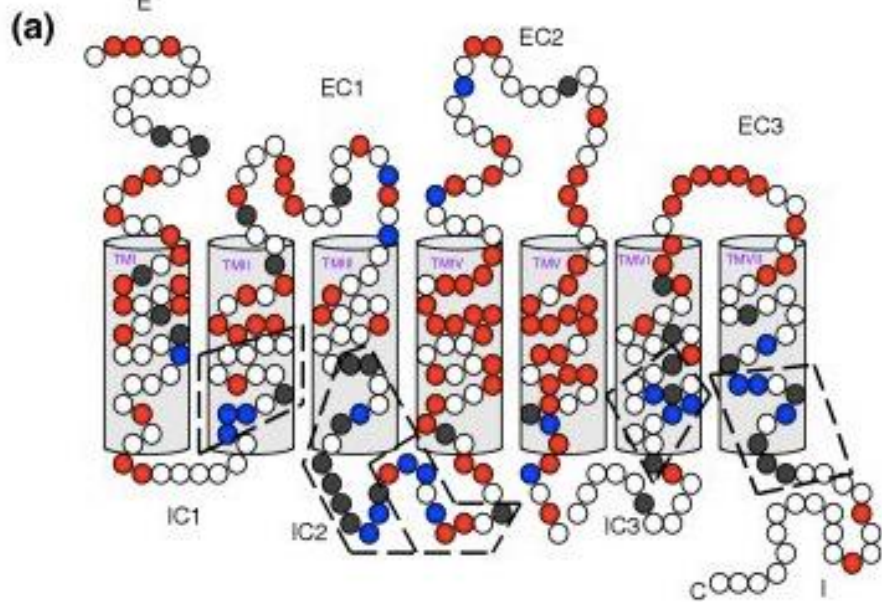
The Olfactory Receptors



Linda Buck, Nobel prize 2004

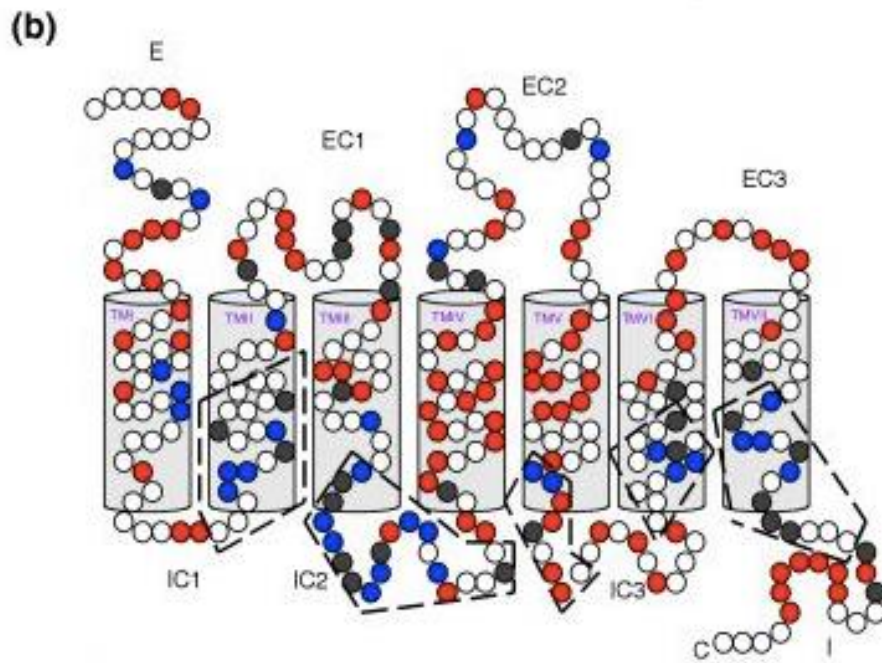


Richard Axel, Nobel prize 2004



Dog

- Highly conserved > 90%
- Conserved > 70%
- Variable > 30%
- Highly variable



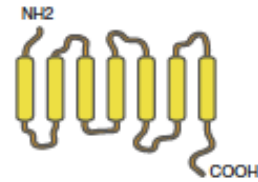
Rat

Quignon et al. 2005

	<i>Rat</i>	<i>Dog</i>	<i>Human</i>	<i>Mouse</i>	<i>Cat</i>	<i>Elephant</i>	Poissons
Intact genes	1234	856	391	913	677	1948	50 À 150
Pseudogenes	311	238	464	296	375	2230	6 à 50
Total	1545	1094	855	1209	1052	4178	
pseudogenes (%)	20%	22%	54%	25%	35%	53%	

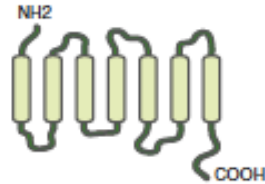
From: Quignon et al. 2005
 Glusman et al. 2001
 Godfrey et al. 2004
 Montague et al. 2014
 Niimura et al. 2014

OR



Main Olfactory Epithelium
Septal Organ

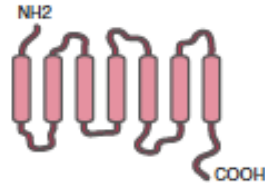
TAAR



Main Olfactory Epithelium
Gruenenberg ganglion

Liberlès and Buck 2006

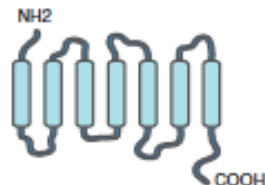
FPR



Vomer nasal Organ

Liberlès et al. 2009
Rivière et al. 2009

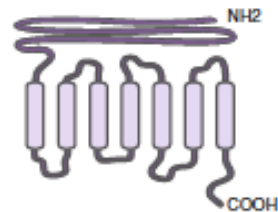
V1R



Vomer nasal Organ

Dulac and Axel 1995

V2R



Vomer nasal Organ
Gruenenberg ganglion

	OR	TAAR	VR1	VR2
Human	400 ¹	9 ²	4 ³	0 ⁴
Rat	1500 ⁵	17 ²	102 ³	90 ⁶
Dog	850 ⁴	2 ⁶	8 ³	0 ⁴
Cat	677 ⁷	-	21 ⁷	-
Tilapia	158 ⁸	44 ⁹	-	-
Zebrafish	143 ¹⁰	58 ¹¹ /109 ¹²	1 ¹³	24 ¹¹ /60 ¹²

1 Malnic et al., 2004, PNAS

2 Lewin AH, 2006, Aaaps J.

3 Grus et al., 2005, PNAS

4 Quignon et al., 2006, Cold Spring Harbor Laboratory Press

5 Quignon et al., 2005, Genome Biology

6 Zhang et al., 2010, Front Neurosciences

7 Mandrague et al., 2014, PNAS

8 Azzouzi et al. BMC genomics, 2014

9 Azzouzi et al. BMC genomics, 2015

10 Alioto et al., BMC genomics, 2015

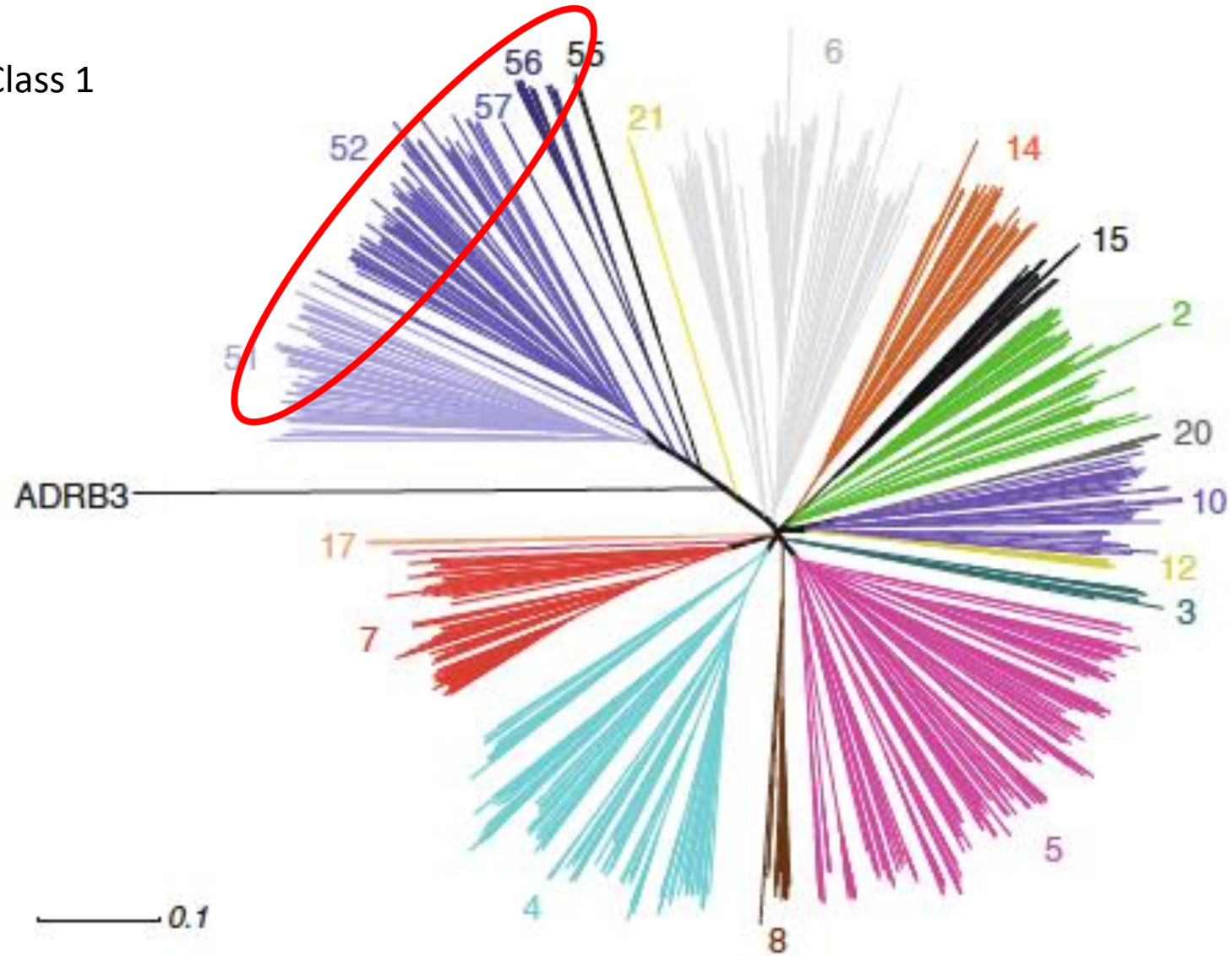
11 Gloriam et al. ,2005, Mol. Phylogenetic Evol.

12 Hashigushi and Nishida, 2005, Gene

13 Pfister and Rodriguez, 2005, PNAS

DOG

Class 1



Class 2

Neighbor-joining tree of dog OR protein sequences.

All putatively functional dog OR sequences were aligned using ClustalX and the tree was generated and drawn using Dendroscope..

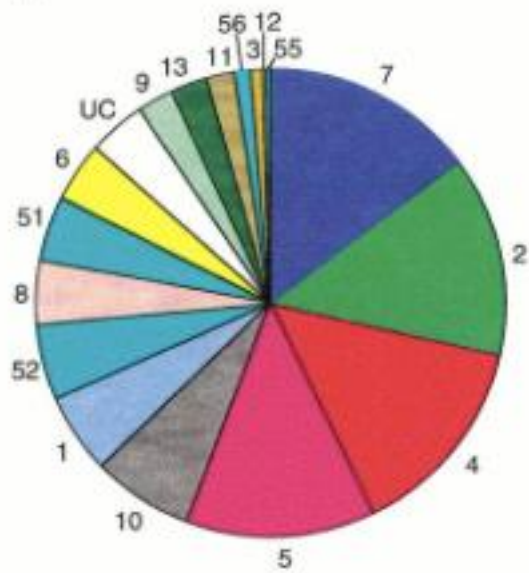
The dog ADRB3 was used as outgroup. The scale bar corresponds to 0.1 AA substitutions per site

ACG.AAA.TGT.TTT.TAT.CGT.TGU.GGT.GCT.AAA.CAC.ACG.CAT

Thr. Lys.Tyr.Phe.Tyr.Arg.Cys.Gly.Ala. Lys. His. Thr. His

ACG.AAA.TGT.TT**C**.TAT.CGT.**C**GU.GGT.GCT.AAA.CAC.ACG.CAT

Thr. Lys. Tyr. Phe.Tyr. Arg. **Arg**. Gly. Ala. Lys. His. Thr. His



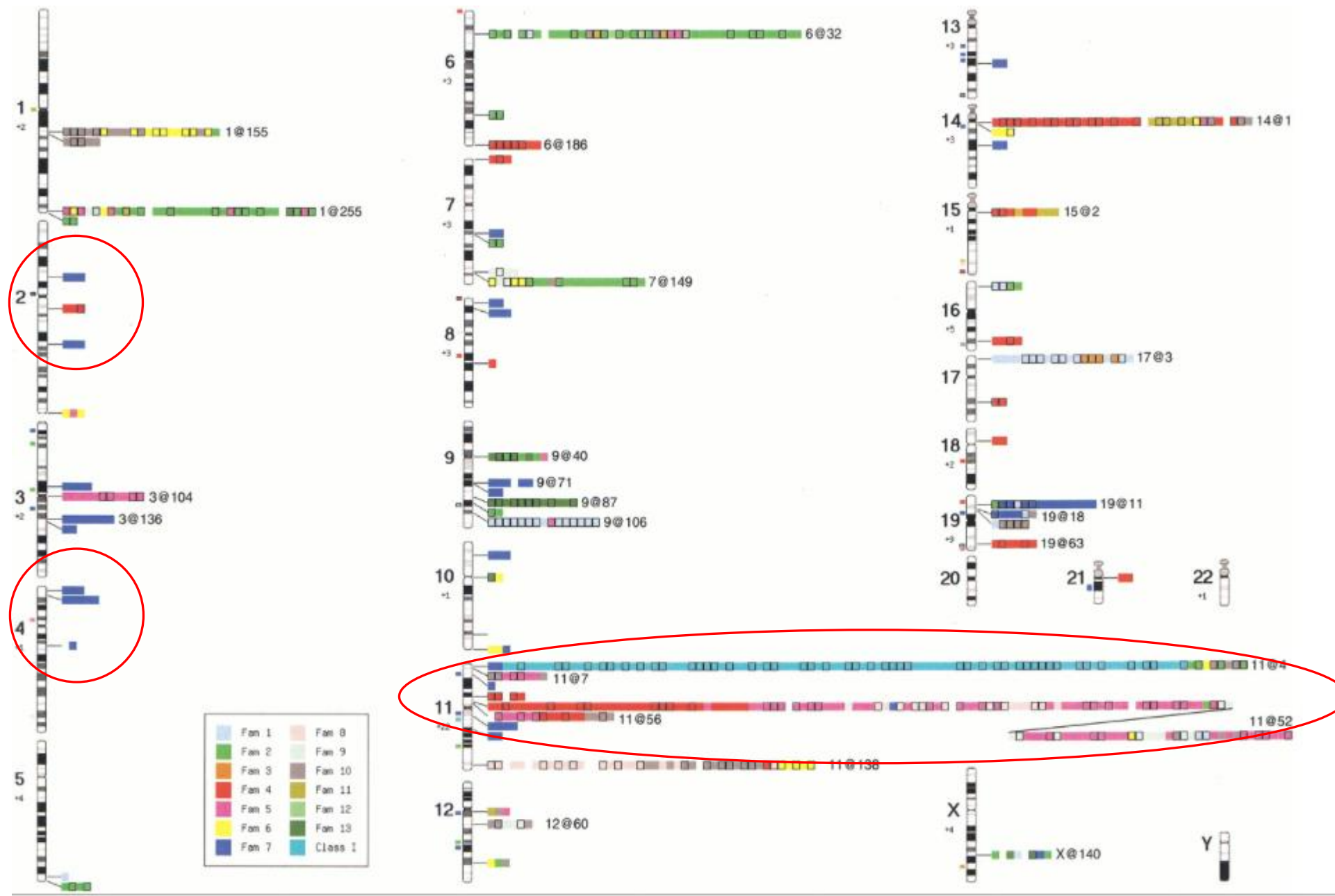
Human family size distribution

Glusman et a 2001

	# classes	# families	# sub-families
Human	2	17	300
Mouse	2	nd	241
Dog	2	23	300
Rat	2	21	282

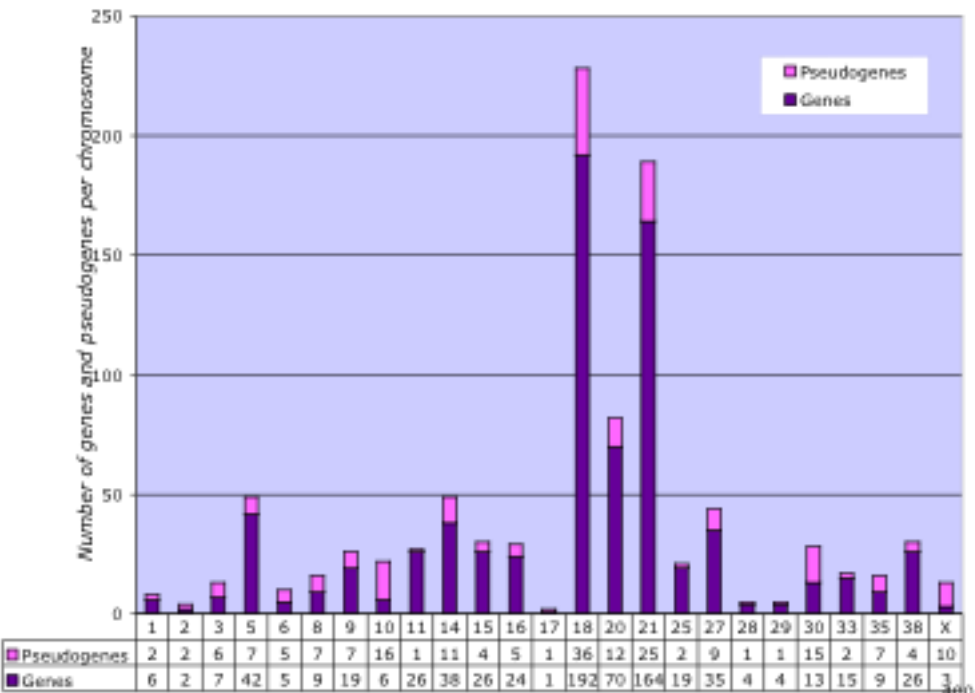
Godfrey et al. 2004
Quignon et al. 2005

Genome Organization



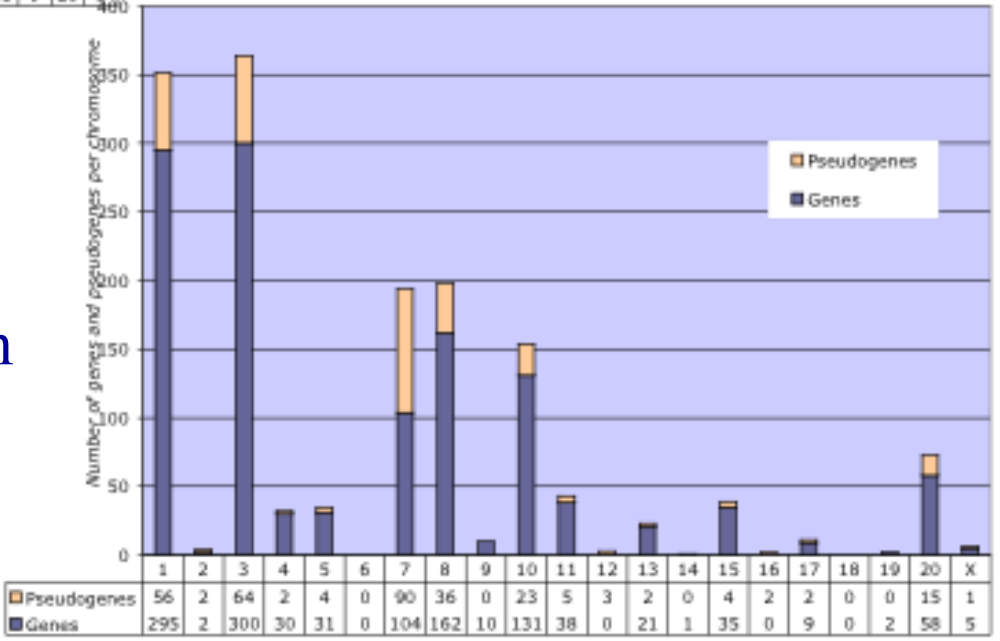
Cfa OR distribution

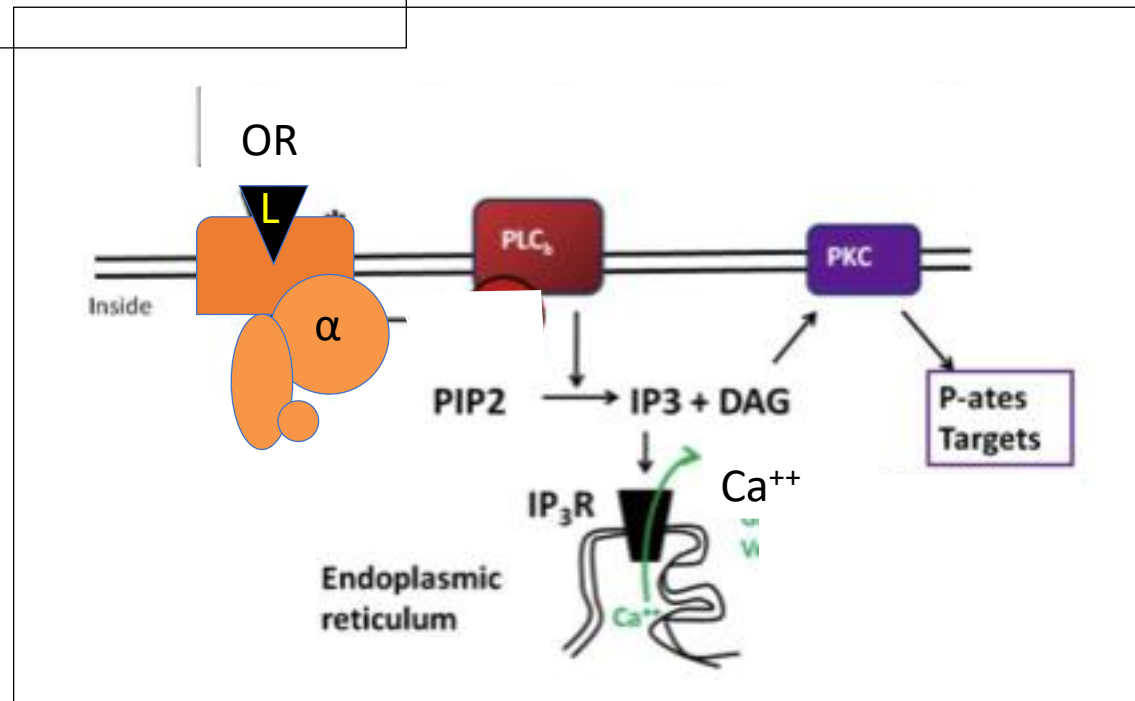
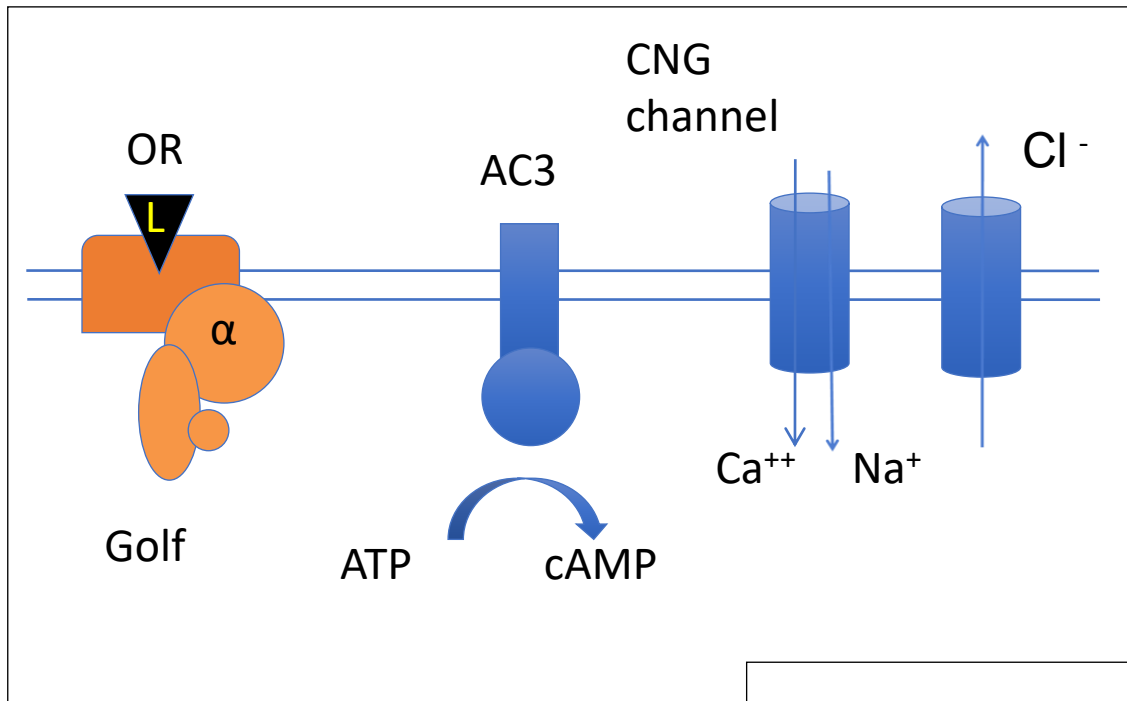
Cfa with no OR gene
 4, 7, 12, 13, 19, 22-24, 26,
 31, 32, 34, 36, 37, Y



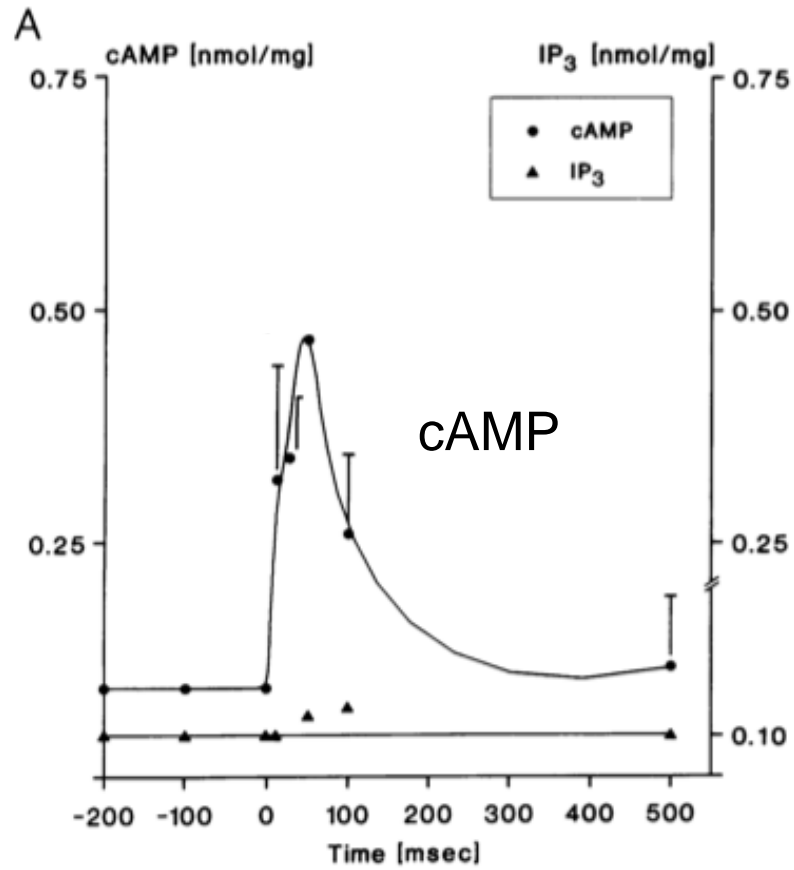
Rno OR distribution

Rno 6, 18 and Y have
 no OR

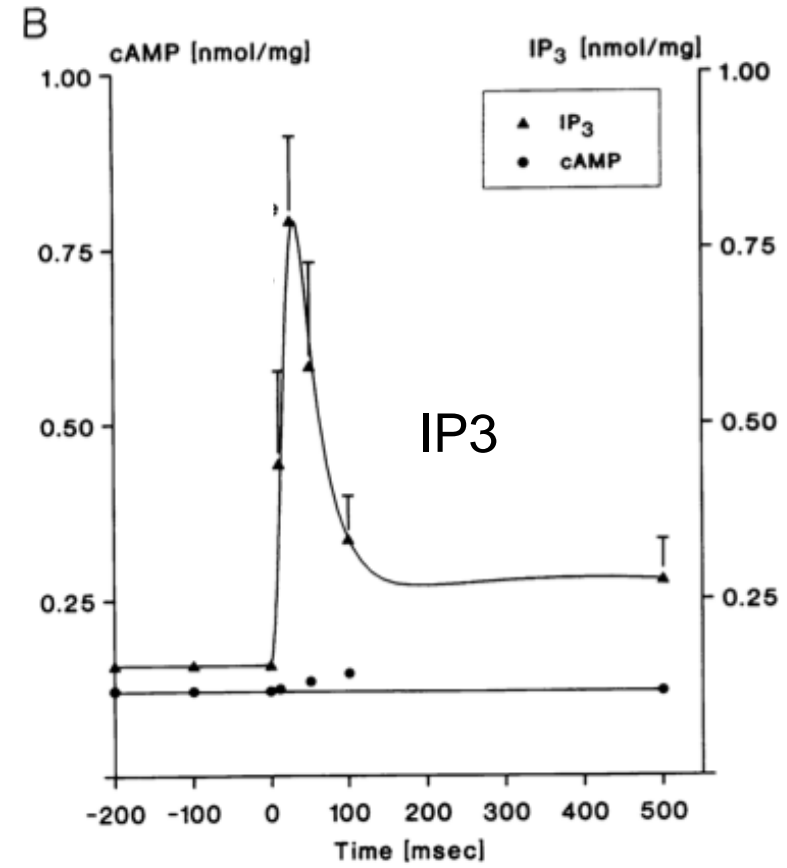




Citralva



Pyrazine



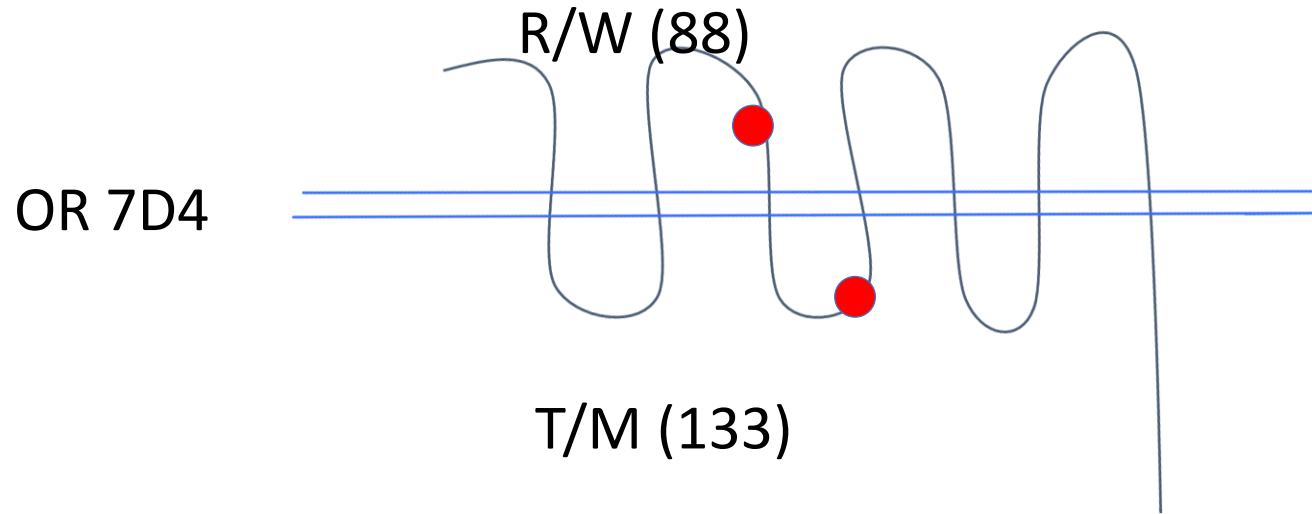
Boekhoff et al. 1990

cAMP and IP₃ rat cilia responses to citralva and pyrazine

- Un OR peut lier différentes molécules chimiques (odorants)
- Une molécule chimique donnée se lie à plusieurs OR différents

Il s'agit d'un **code combinatoire**

Polymorphisme et fonctionnalité



RT = good responder

WM = poor responder

In vitro

In vivo

28% RT/RT people do not detect androstenone
46% RT/WM people do not detect androstenone

The RT/RT group detect androstenone at lower concentration 1/16

RT/WM people find androstenone less unpleasant, than the RT/RT people

Chez le chien

Fréquence moyenne des SNP dans les gènes OR = 1 SNP/529nt

Fréquence moyenne SNP dans les autres gènes 1 SNP / 8631 nt

Expression des OR (c.a.d. DNA RNA Protéine)

- Un seul des deux allèles est exprimé par OSN
- Mais les deux sont exprimés

Chess A, Simon I, Cedar H, Axel R:

Allelic inactivation regulates olfactory receptor gene expression. *Cell* 1994, 78(5):823-834.

Ishii T, Serizawa S, Kohda A, Nakatani H, Shiroishi T, Okumura K, Iwakura Y, Nagawa F, Tsuboi A, Sakano H:
Monoallelic expression of the odourant receptor gene and axonal projection of olfactory sensory neurones.

Genes Cells 2001, 6(1):71-78.

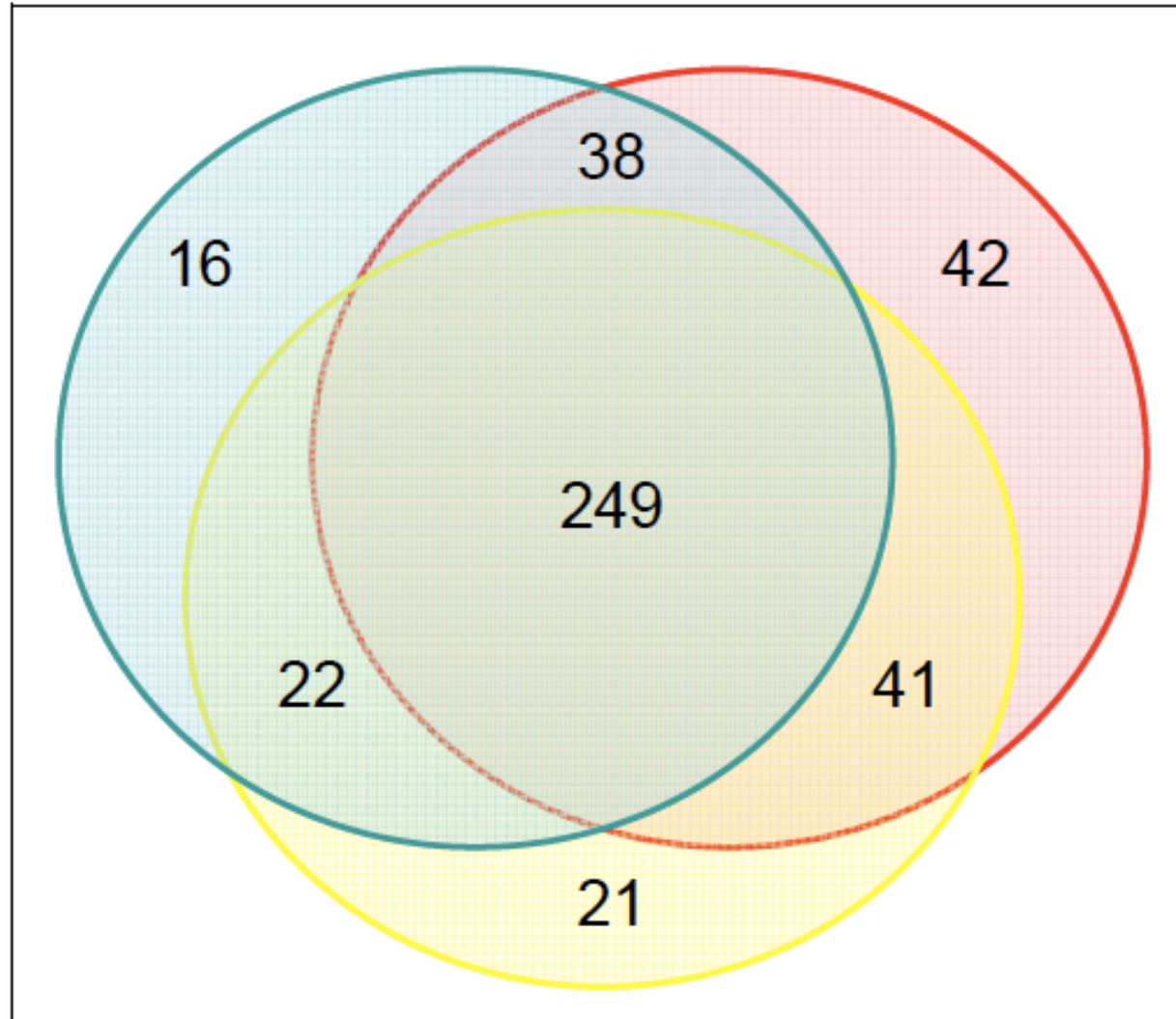
Deep Sequencing of the Murine Olfactory Receptor Neuron Transcriptome
 Kanageswaran et al. Plos One 201

FPKM	>50	> 10	>1	>1.10 ⁻⁵	0
OR	5	138	672	116	168

Genes	OSN
Olfr 1507	89
Olfr 533	83
Olfr 166	71
Olfr 1264	66
Olfr 727	56

<u>Omp</u>	1185
Gng13	1112
<u>Gnal</u>	1072

333



370

Figure 3

The number of predicted human OR genes whose expression was detected (at $P < 0.05$) in one or more of the three olfactory epithelium (OE) samples. As can be seen, there is a substantial difference in the expressed OR gene repertoire of each of the three OE samples.

- Il existe de grandes différences quantitatives et/ou qualitatives de perception olfactive entre individus

Questions:

Pourquoi certains OR sont exprimés et pas d'autres?

Quel mécanisme ou facteurs sélectionnent l'OR à exprimer par un OSN donné ?

Les gènes exprimés et leur niveau d'expression sont –ils modulables en fonction des circonstances?

- **Obstruction nasale**

rhinite, congestion, inflammation des sinus etc

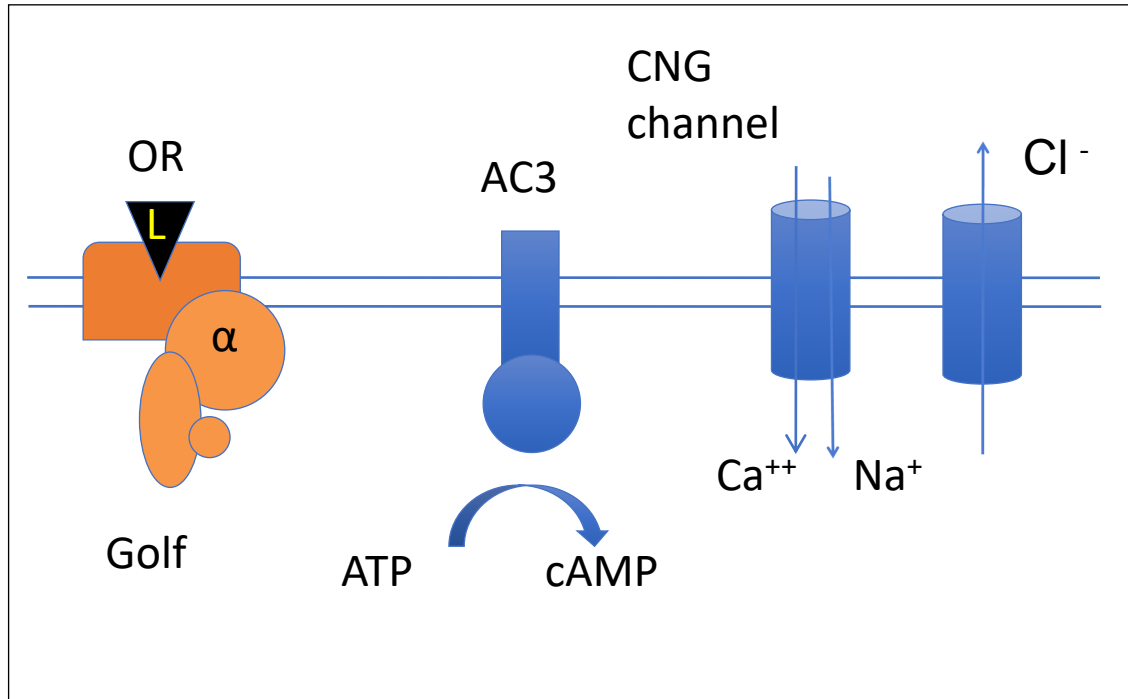
- **Problèmes Sensoriels**

fumeurs actifs ou passifs (risque important)

- **Disfonctionnement cérébral**

Alzheimer and Parkinson.

cAMP pathway



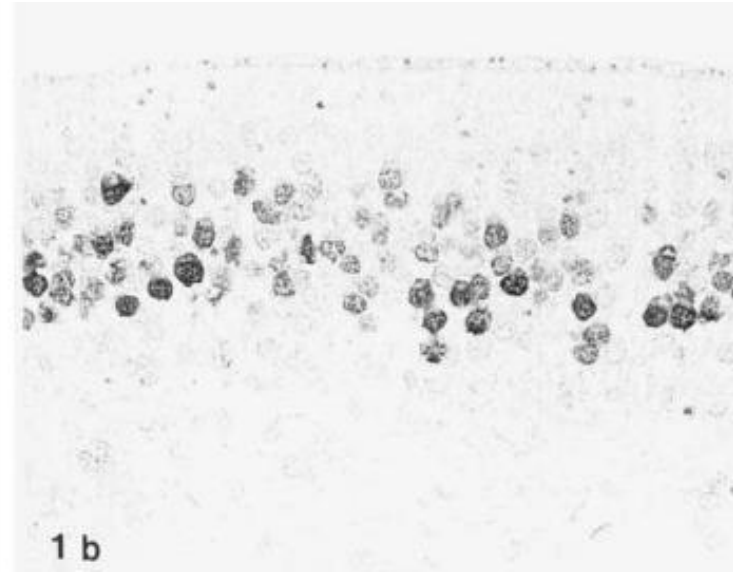
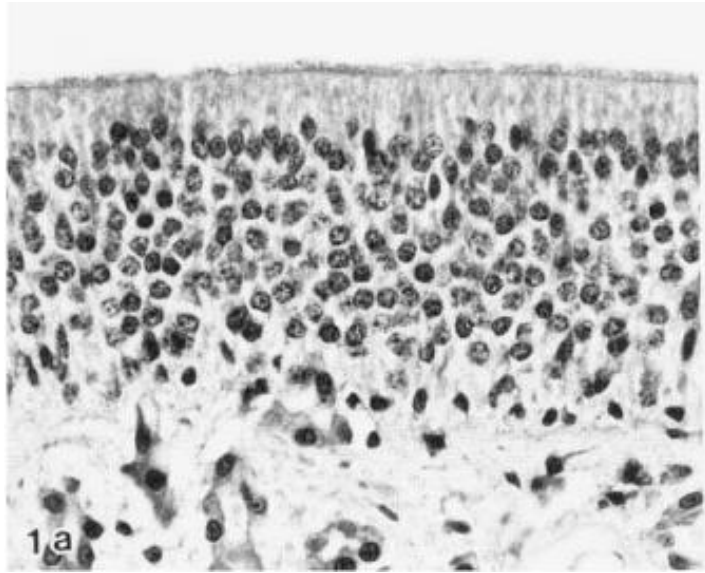
En cas d'odeur persistante

On observe une désensibilisation

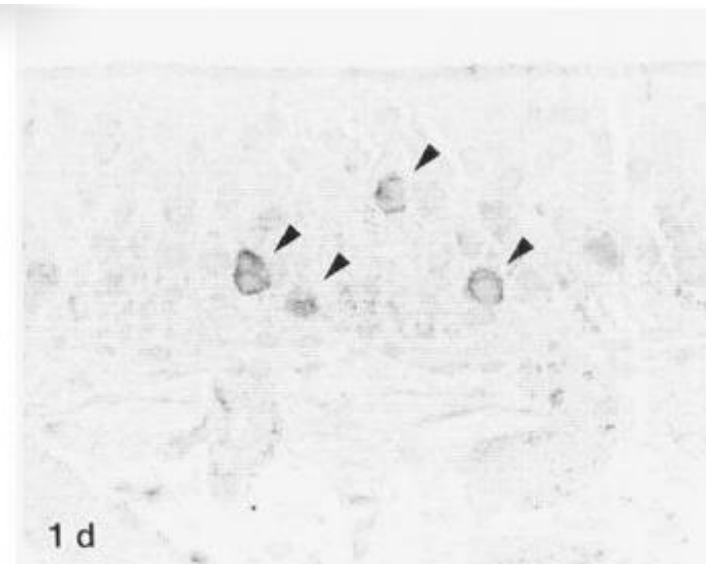
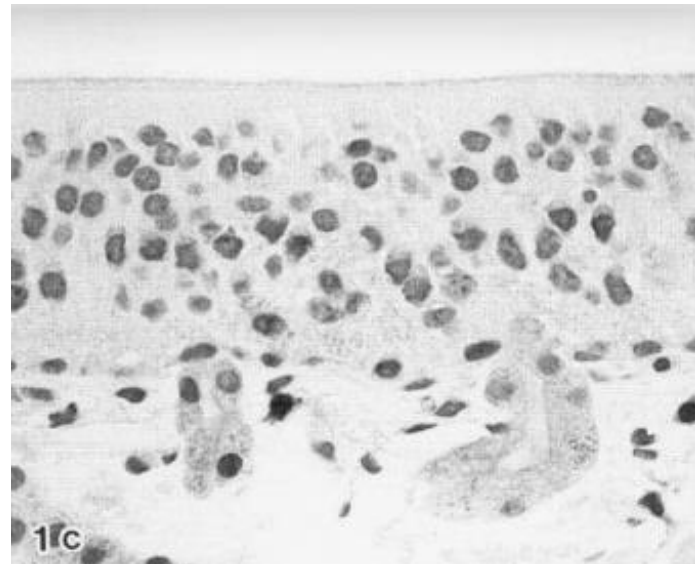
ou

Une accoutumance

Age related changes in the dog olfactory epithelium



10 years



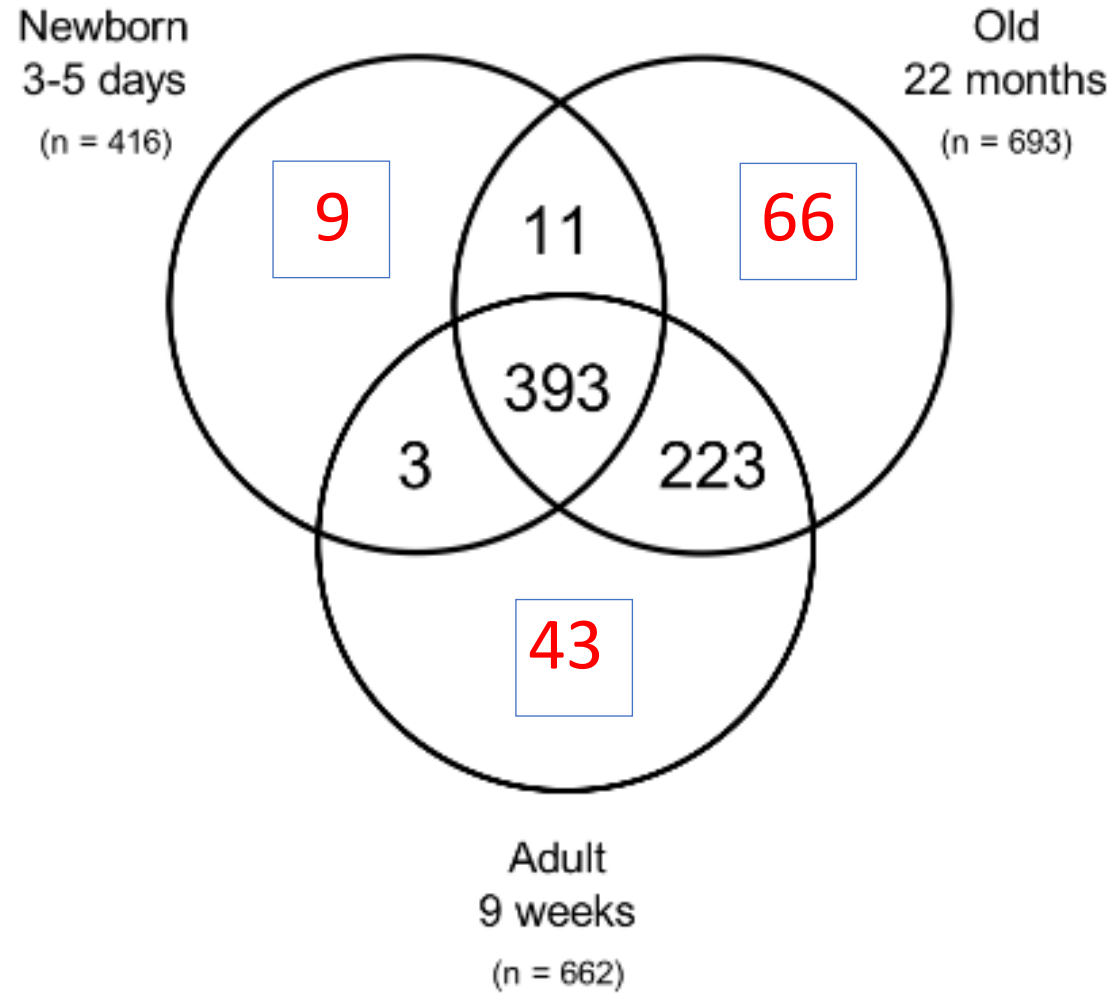
19 years

Olfactory Epithelium

OSN

Hiral et al 1995

B Expressed olfactory receptor genes



The Claus Wedekind experiment: MHC and sexual selection

Wedekind, C. et al. (1995). "MHC-dependent preferences in humans".
Proceedings of the Royal Society of London **260 (1359): 245–49.**

Le complexe majeur d'histocompatibilité (MHC) est un groupe de gènes important de reconnaissance tissulaire

Il existe une forte tendance à maintenir un certain niveau d'hétérogénéité, souvent gage de meilleure résistance aux agents pathogènes et partant un impact sur la sélection sexuelle

D'où l'hypothèse de travail émise par Claus Wedekind et Sandra Furi:

Est-ce que l'odeur personnelle favorise certaine combinaison de MHC ou plus simplement l'hétérogénéité ?

Plan expérimental:

6 T-shirts portés par 2 femmes et 4 hommes sont donnés à humer à 121 sujets hommes et femmes et à classer en fonction de leur odeur plaisante ou désagréable

Résultats :

une nette préférence l'odeur est corrélée à l'hétérogénéité du MHC entre le celui du porteur de T-shirt et le sujet

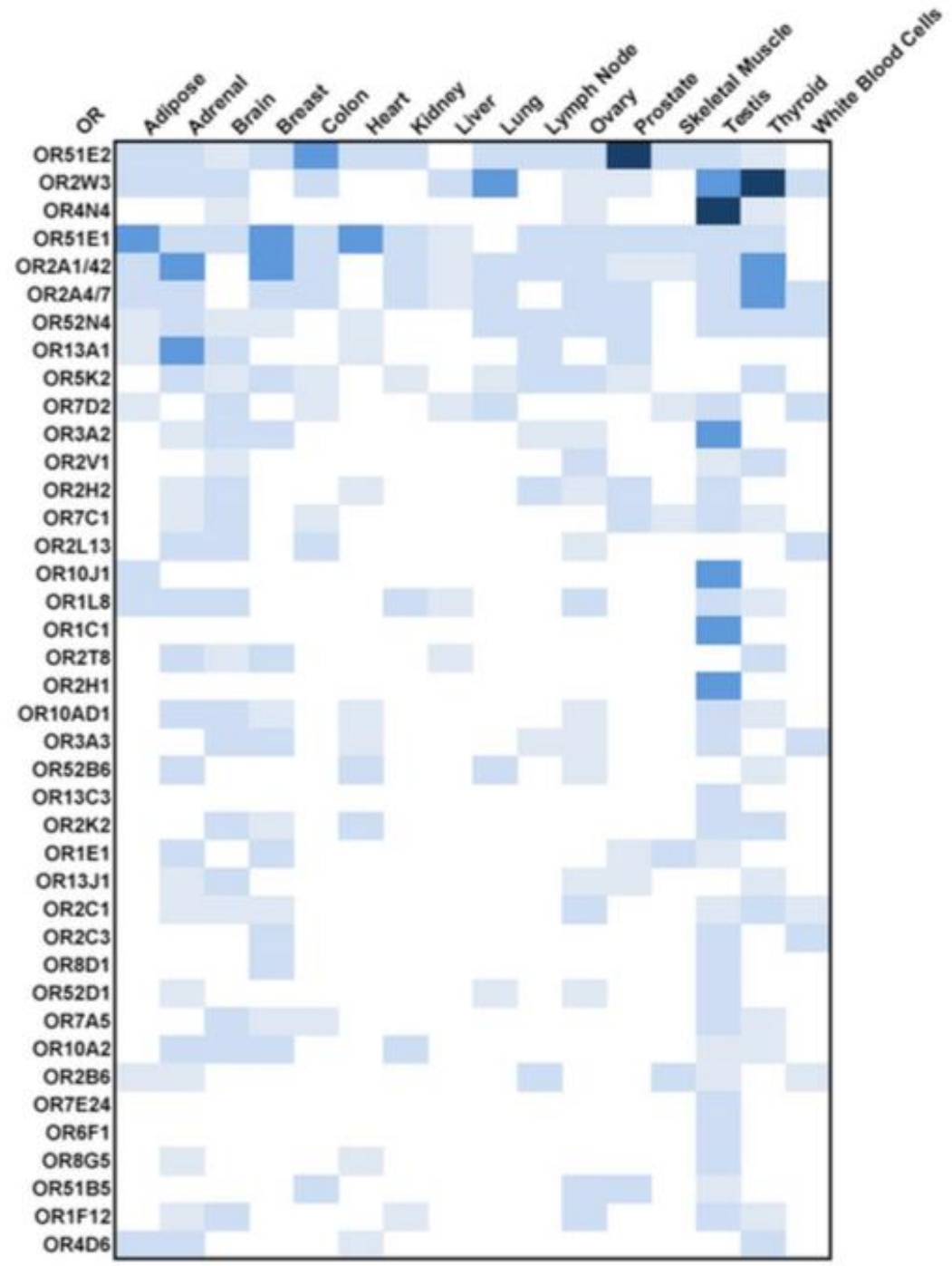
- De nombreuses questions restent en suspend aussi bien sur l'efficacité de ce sens que sur l'impact de l'odorat sur le comportement individuel

MAIS

Ectopique Expression des OR

M. Parmentier *et al.*, *Nature* **355**, 453 (1992).

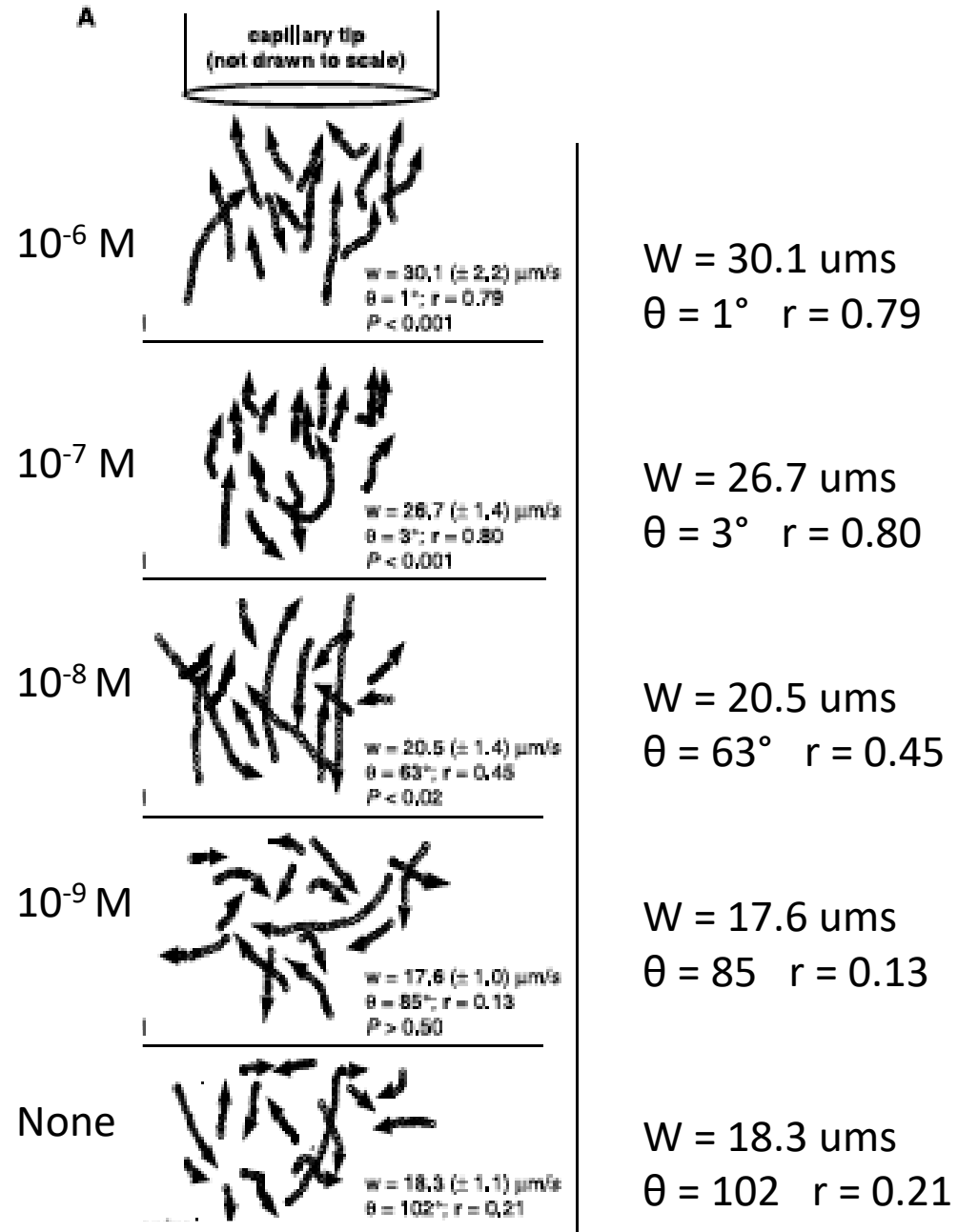
P. Vanderhaeghen *et al.* *J. Cell Biol.* **123**, 1441 (1993).



Flegel et al 2013

Swimming behaviour of human sperm near a microcapillary tip filled with bourgeonal, aligand to hOR17-4.

Speed and direction were measured by computer-assisted video motion analysis [CAVMA



- Quel est le véritable ligand d' hOR17-4?
- Produit par quelle cellule?
- Quel serait le rôle des autres OR ?

Olfaction et Diagnostic

Melanome

Diabète

covid etc

En guise de conclusions

Fonction vitale pour tous

L'olfaction :
un domaine passionnant et riche de questionnement

Les prouesses olfactives de nombreuses espèces nous laissent
pantois

Peu ou pas soutenue financièrement

REMERCEMENTS

CNRS

UNIVERSITE de RENNES

AKC,NIH,US ARMY,TSWG,DARPA

Société
d'Encouragement
pour l'industrie
nationale FONDÉE EN 1801

AFAS



IESF
SOCIÉTÉ DES INGÉNIEURS ET
SCIENTIFIQUES DE FRANCE
ÎLE-DE-FRANCE

ABG
Association
Bernard Gregory



Calice Becker

Parfumeur, Directrice de l'Ecole de parfumerie Givaudan

Eco-
Learn

MR21

e5t





GIVAUDAN PERFUMERY SCHOOL

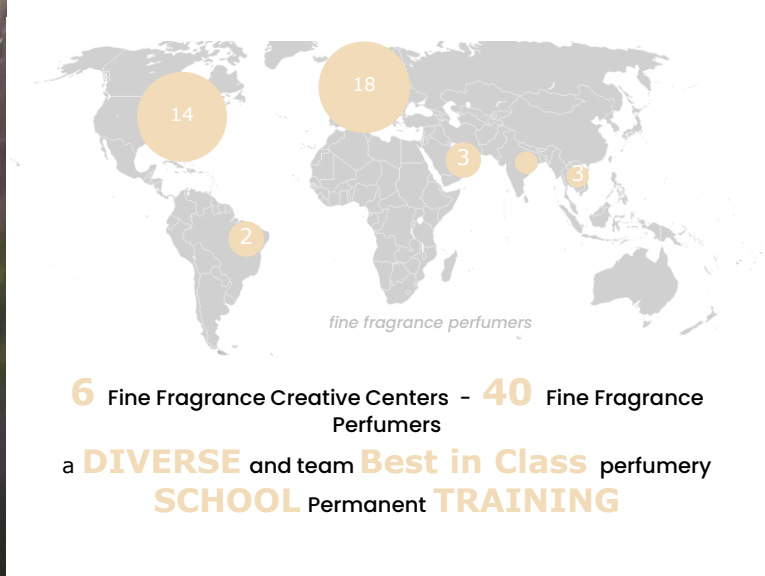
PDSI 16 JUIN 2022





THE SCHOOL, A PILLAR OF THE GIVAUDAN CULTURE

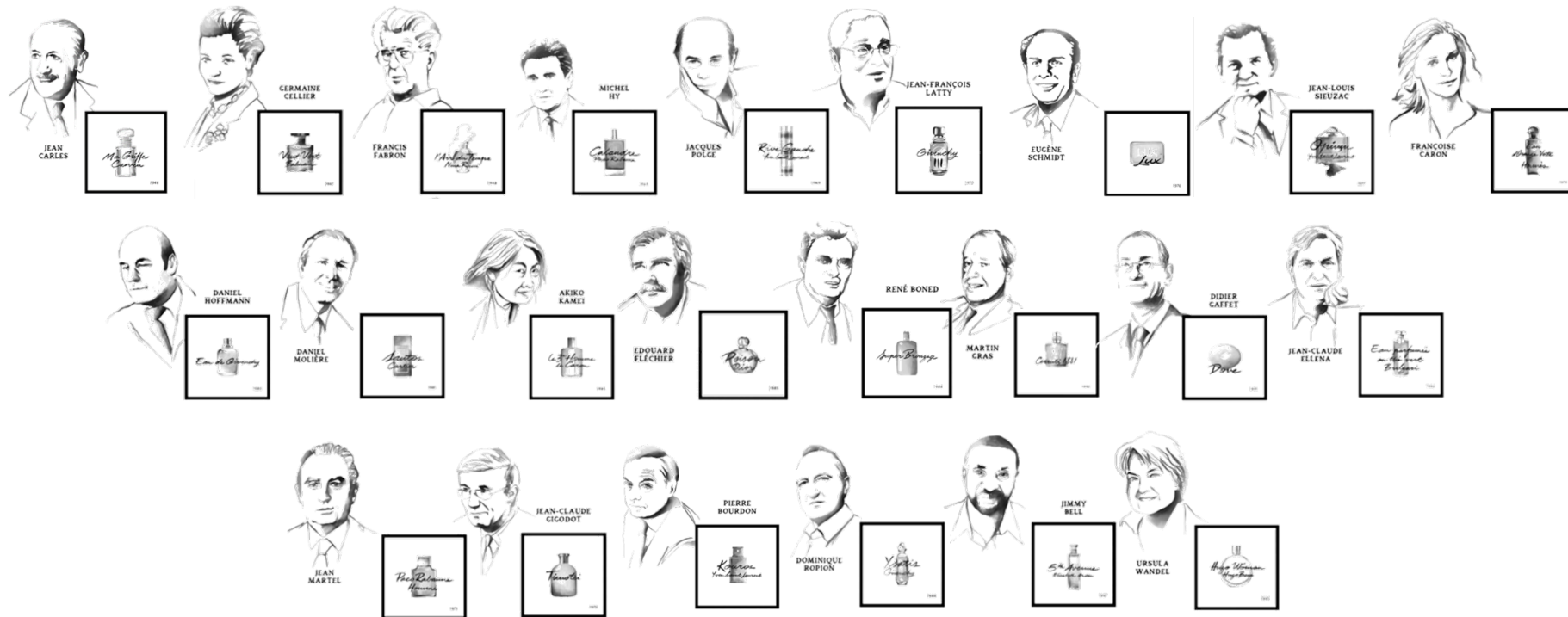
ONE PERFUMERY SCHOOL,
TWO CAMPUSES (Argenteuil & Singapour)
AND KEY FIGURES



2-3 New students every year	10 Students currently at the PS	100 First -round interviews
2500 Candidates to the Perfumery School	70% of Givaudan Perfumers trained with the Perfumery School method	

A BEAUTIFUL LEGACY FROM ROURE FROM 1946 TO 2019

TRAINING THE MOST TALENTED PERFUMERS





THE JEAN CARLES METHOD FOR INGREDIENTS CLASSIFICATION

RAW MATERIALS
(Natural & Synthetic)



LEARNING
BY CONTRASTS

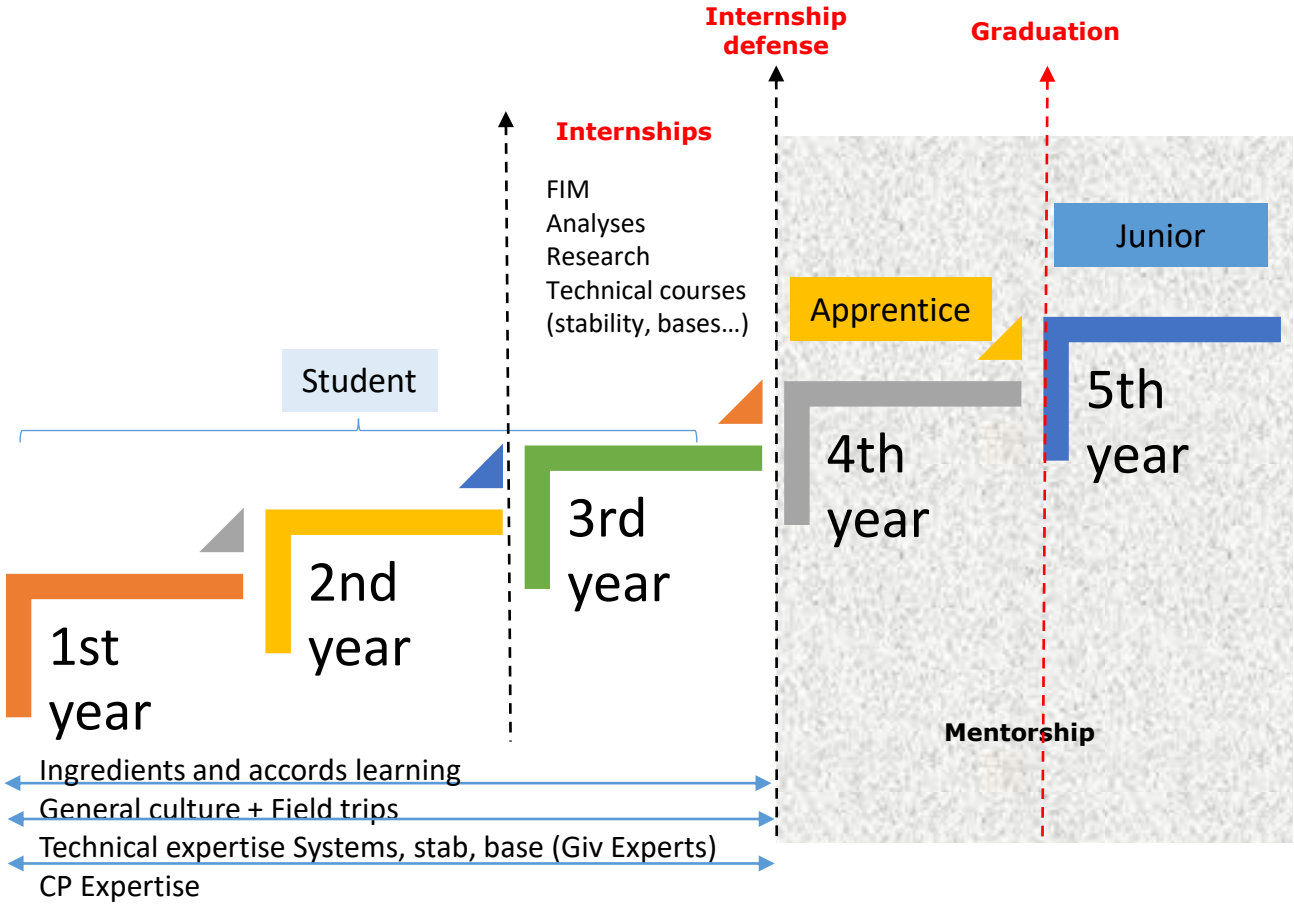


LEARNING
BY SIMILARITIES

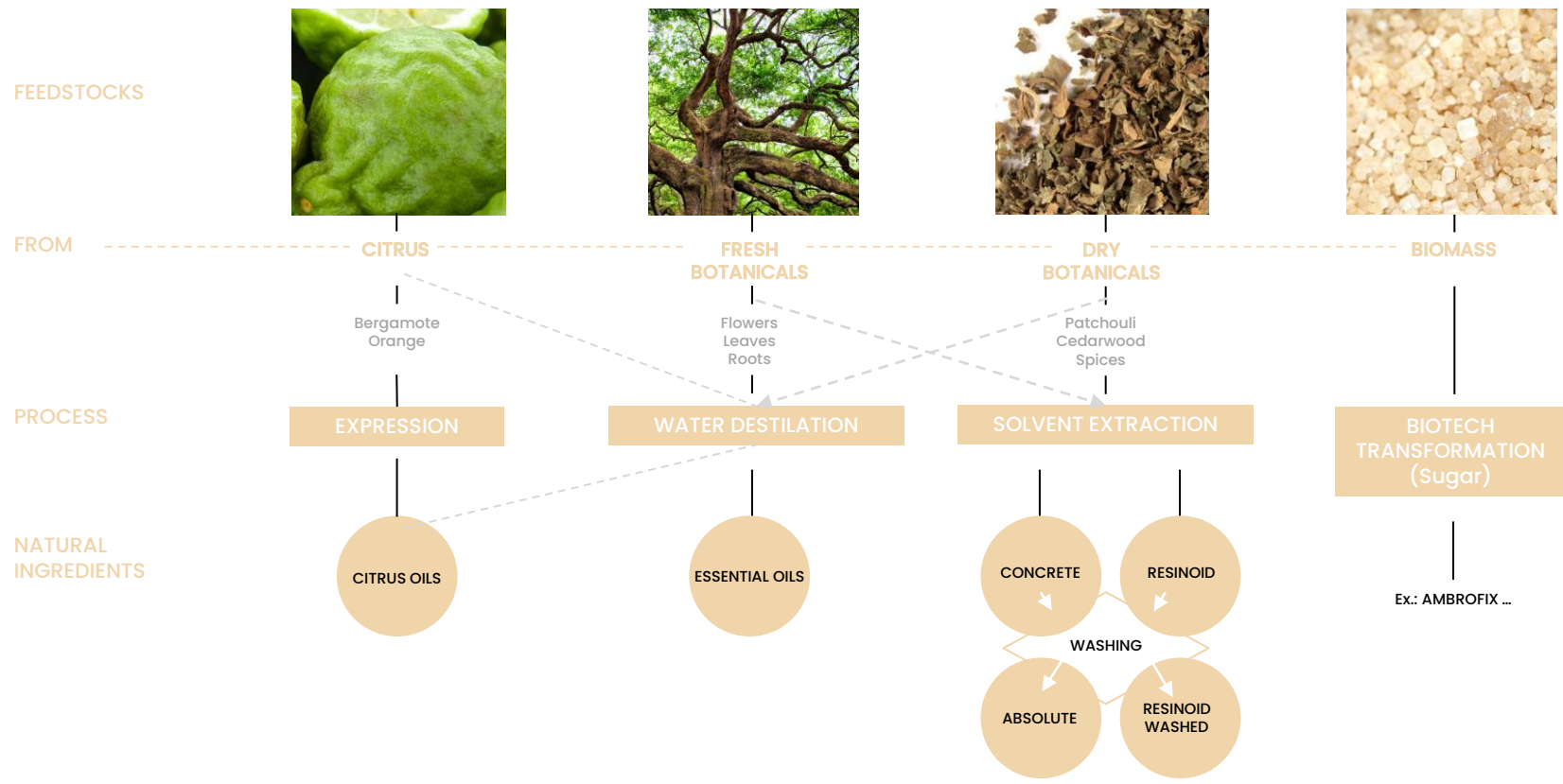
In the 1950s, a Roure perfumer named Jean Carles developed a method for studying and combining perfumery materials.

This method is still in use in Givaudan's perfumery school and has become a standard for the whole industry

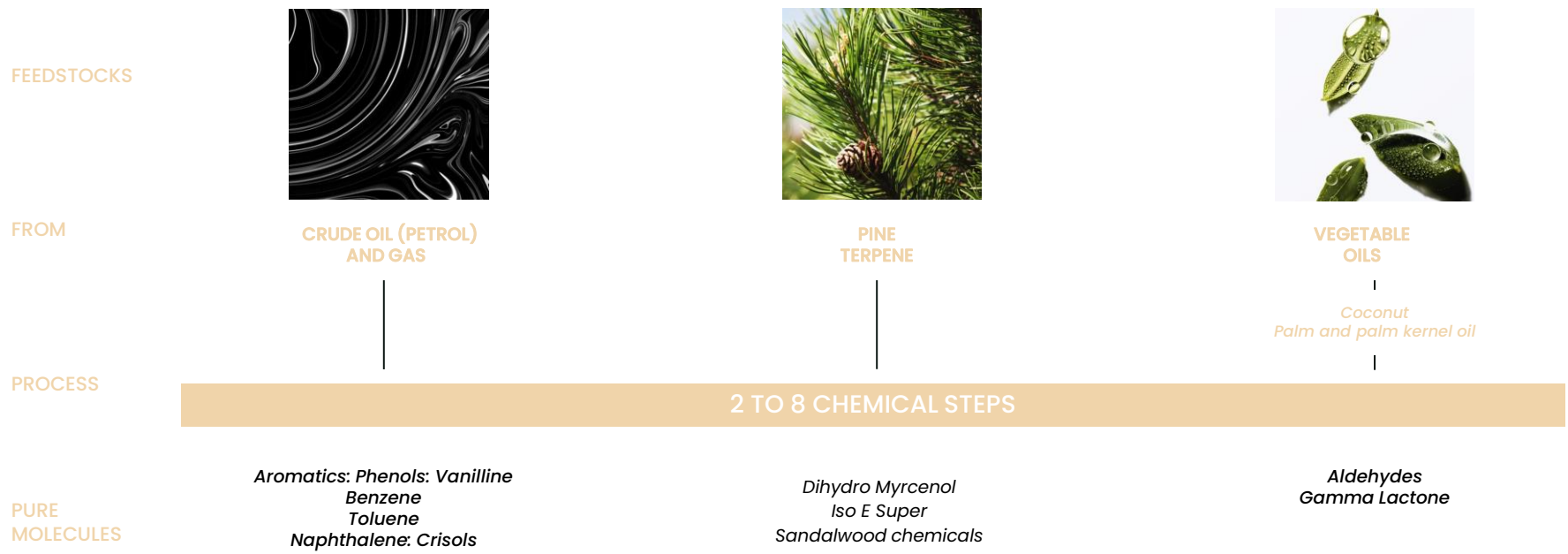
DEVELOPMENT OF A YOUNG PERFUMER

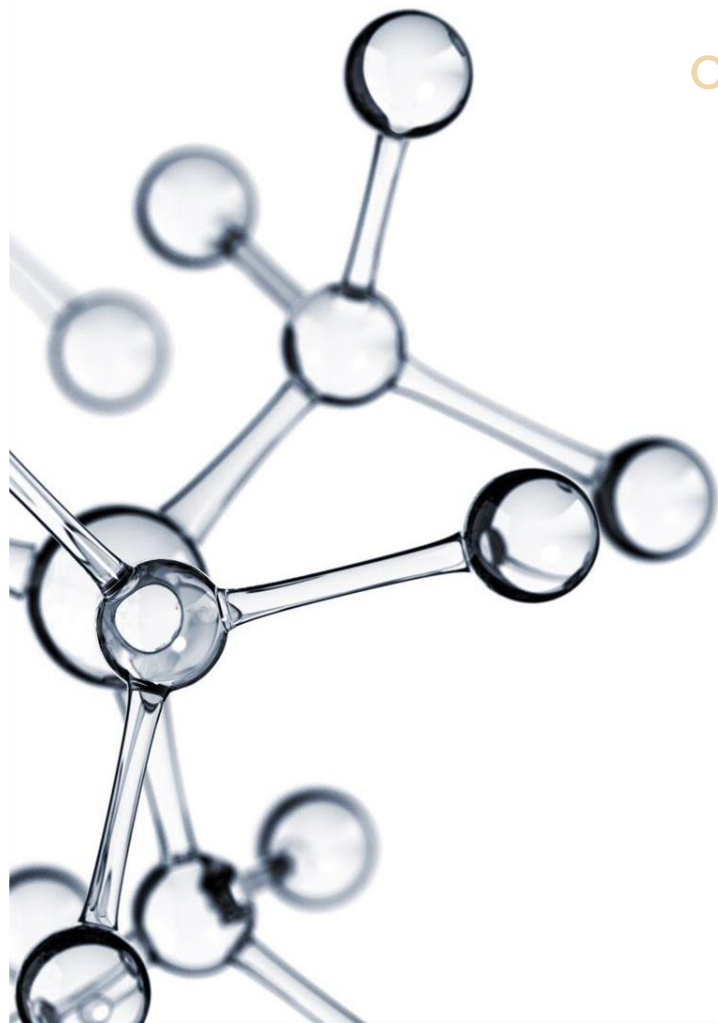


WHERE OUR INGREDIENTS COME FROM ... ?



WHERE OUR INGREDIENTS COME FROM ... ?





CHEMICAL INGREDIENTS

MOLECULES

*Why
Molecules ?*

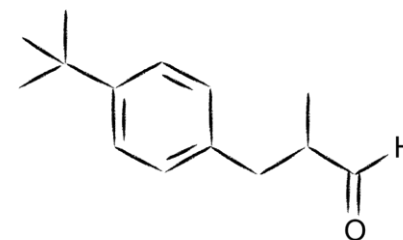
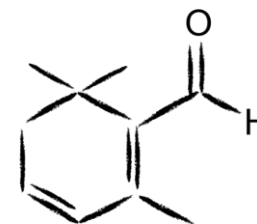
BETTER STABILITY



ASSURED SUPPLY, CONSISTENT
QUALITY



HIGH CREATIVE VALUE





HOW TO SMELL?

An appropriate gesture
An appropriate material



SENSE OF SMELL A HOLISTIC EXPERIENCE

CONTEXTUALIZATION

Vision (and touch,
sound)
influences the
judgement

I.e.. Advertising



FAMILIARITY

Enhances positive
experience
(reassurance)

Can be negative if its to
familiar (too common)

I.e.. Smell of your home



HABITUATION

Current signal
Numness

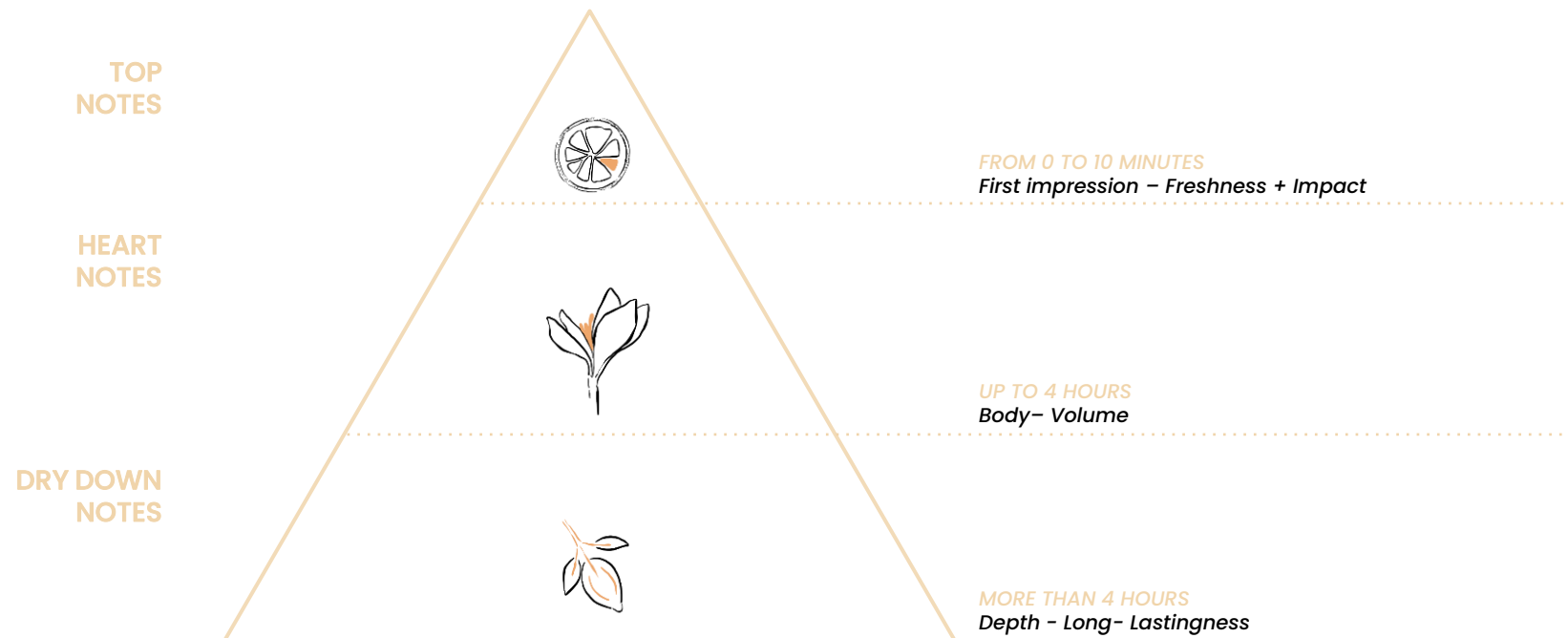
I.e.. own B.O, own fragrance

Like for any senses
Sound of Manhattan's sirens

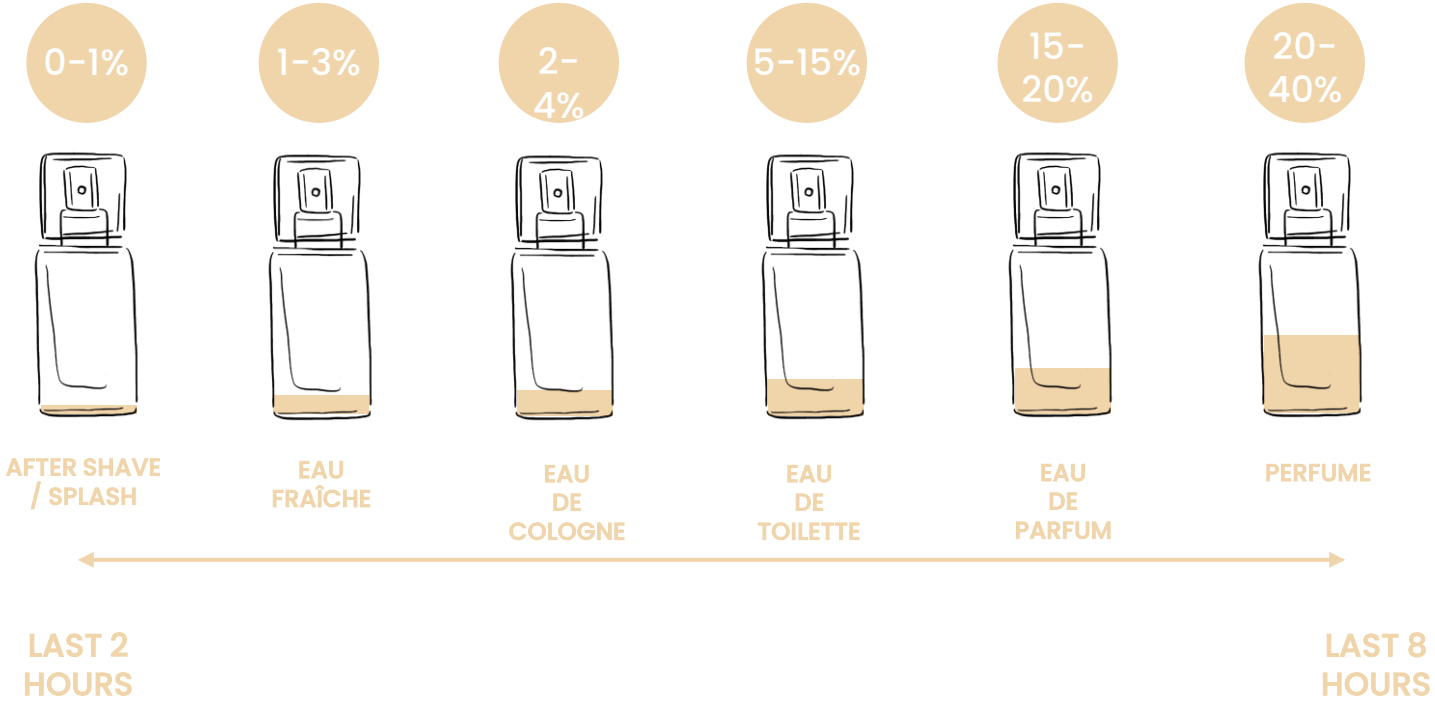


FRAGRANCE STRUCTURE

EVAPORATION STAGES & SENSORY IMPACT



A STORY OF CONCENTRATION



A UNIQUE CURRICULUM

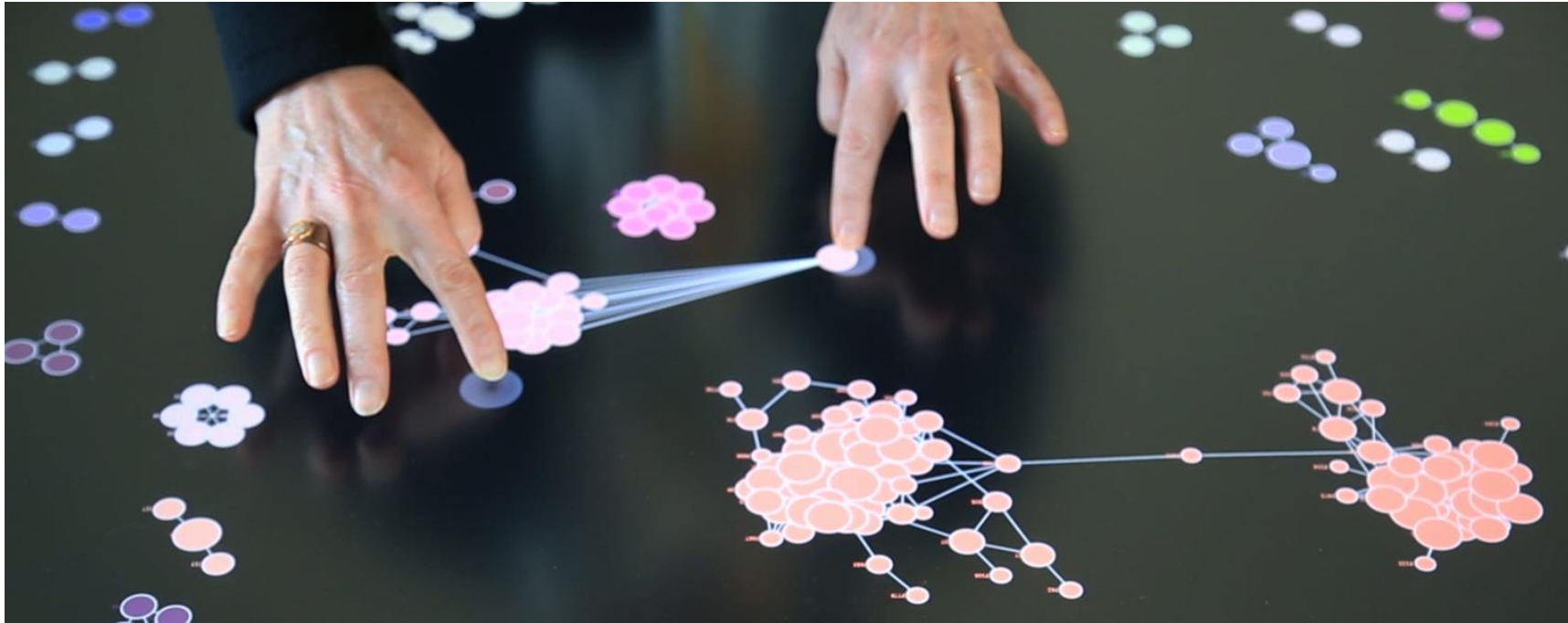
E-gredients



Based on the most recent innovations in terms of memorization, the new e-gredients tool developed for the Givaudan Perfumery School students is a learning platform that enables them practice about **over 500 raw materials** in a self-motivated way.

A UNIQUE CURRICULUM

The formulation of tomorrow



"Innovation has always been at the heart of Givaudan's strategy. We are constantly looking for ways to leverage technological developments to enhance the way we work, and to delight our customers and consumers."

Calice Becker, VP Perfumer and Director of the Perfumery School

A UNIQUE CURRICULUM

Learn & Share

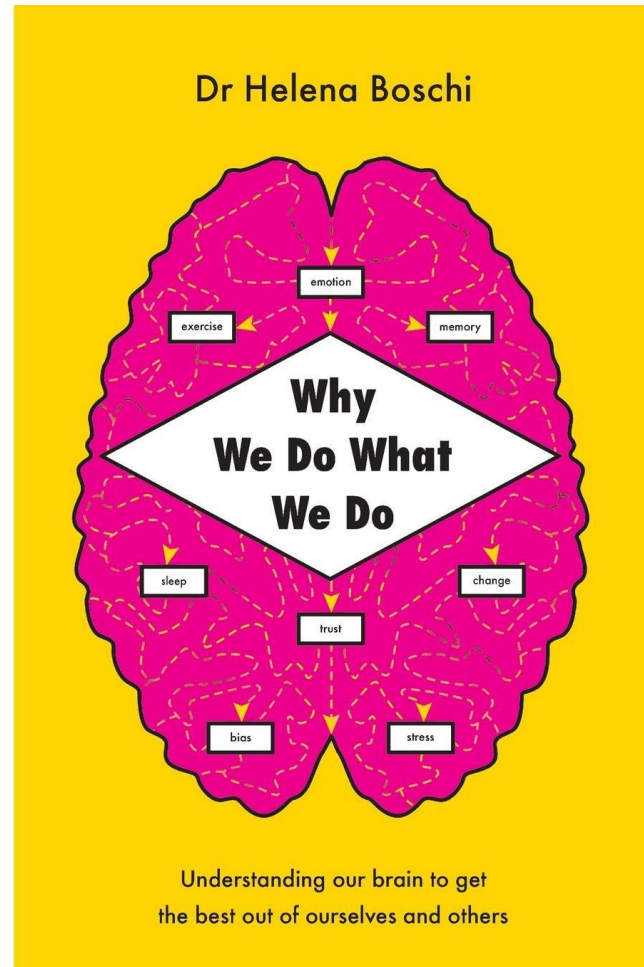


HOURS

At all stages of their training at the Givaudan Perfumery School the students are encouraged to collaborative learning through exercises such as the Learn & Share sessions.

A UNIQUE CURRICULUM

Developing soft skills



A UNIQUE CURRICULUM

Making the most of Givaudan resources



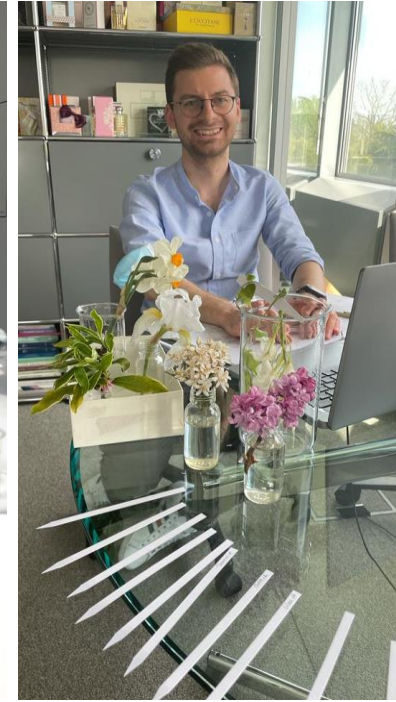
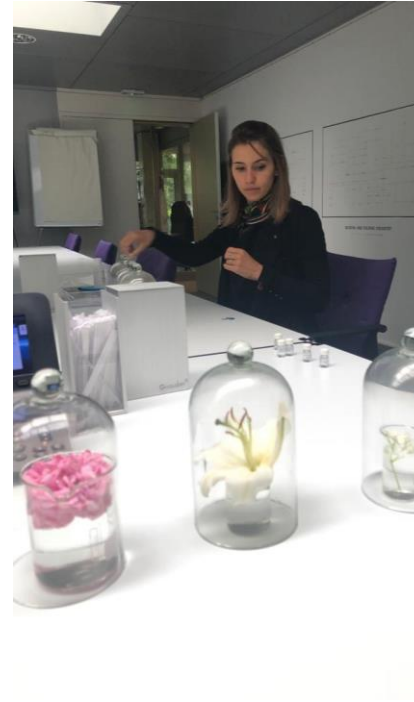
A UNIQUE CURRICULUM

A culture of curiosity



WITH LOVE FOR NATURE

Creating from nature



Since 2018 the students of the Givaudan Perfumery School can work their accords from nature thanks to the "Garden of Scents" and "Garden of Flavors" that give them an immediate access to more than 200 species of fragrant plants (among which 100 species of roses).

WITH LOVE FOR NATURE

Understanding the beauty of raw materials



A GATEWAY TO THE ASIAN MARKET

The Singapore Campus



THE MISSIONS OF THE GIVAUDAN PERFUMERY SCHOOL

Training external and internal stakeholders



BUSINESS PERSPECTIVES

INDUSTRIAL PERSPECTIVES AROUND THE SCENT

The Perfumer



INDUSTRIAL PERSPECTIVES AROUND THE SCENT

The Evaluator



INDUSTRIAL PERSPECTIVES AROUND THE SCENT

The Flavorist



PARKINSON'S SMELL TEST EXPLAINED BY SCIENCE



MA MADELEINE



The Problem :

During the Covid-19 pandemic, the medical community noticed that the sense of smell could be durably affected by the virus. More specifically, as patients regenerate slowly their sense of smell, they have to face partially or completely « new » odorants perceptions different from their smells memories, and sometimes unpleasant (paromia). Our scientists team has found that these patients olfactory dysfunction takes on central olfactory impairments properties.

Our Solution :

Onepoint, Givaudan, the Nice University Hospital and the Université Côte d'Azur have joined forces to create Ma Madeleine, a protocol dedicated to rehabilitating the sense of smell by taking into account the semantic aspects of odors. It includes an olfactive kit containing 12 high fidelity odorants and a Web-App used to guide the training at home.

Our ambition :

Deliver a qualitative and effective smell reeducation experience to the millions of people affected by smell impairment.



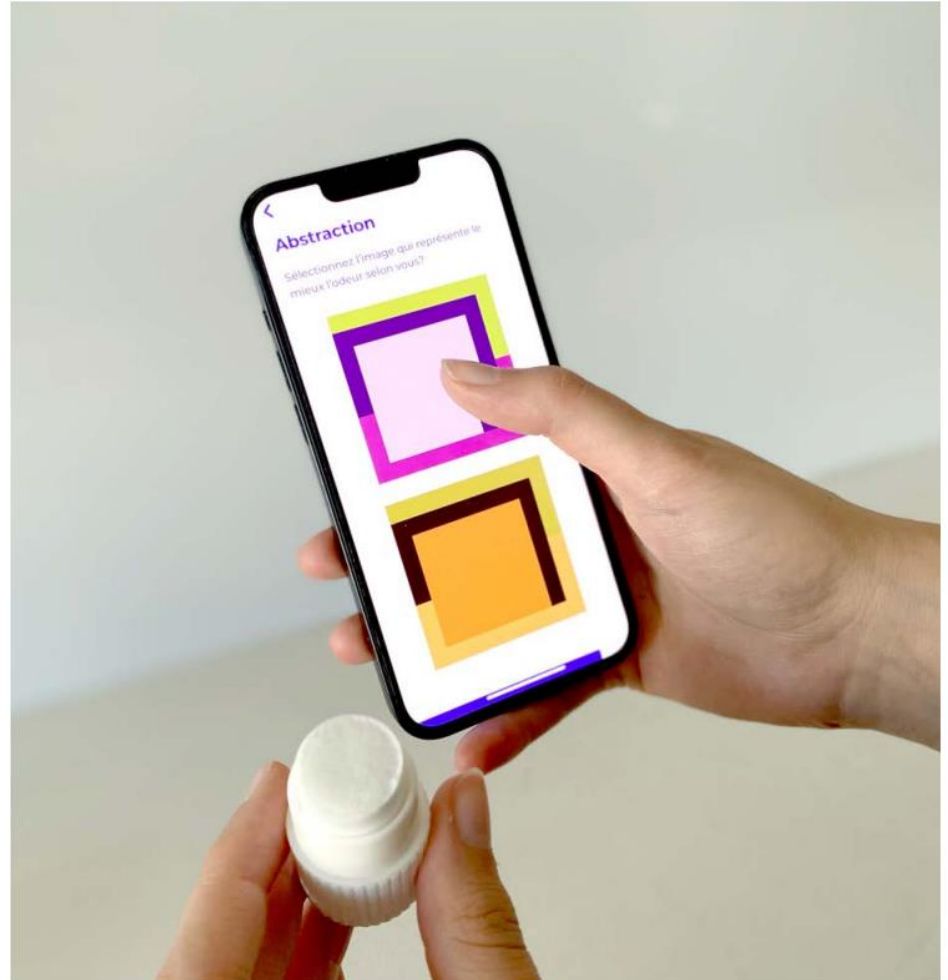
Givaudan

onepoint.

UNIVERSITÉ
CÔTE D'AZUR

Centre
Hospitalier
Universitaire
de Nice

MA MADELEINE



MA MADELEINE

THE VOLUNTEER TEAM



Calice BECKER
VP Perfumer, Head of Givaudan
Perfumery School
GIVAUDAN



Samuel BERNIER
Leader Design and Innovation
ONEPOINT



Xavier FERNANDEZ
Chemist
Innovation and research
Vice-President
UNIVERSITÉ CÔTE D'AZUR



**Auriane GROS et
Magalie Payne**
Neuroscientist et Orthophoniste
CHUN



Clair VANDERSTEEN
ENT surgeon
CHUN



Thank you!
Calice Becker

Follow us on social media

[@givaudan](#)



Givaudan
Human by nature

Cycle : Pour le Développement des Sciences et de l'Innovation (PDSI)
au service des Transitions

QUESTIONS-REPONSES



L'olfaction, une fonction vitale ?

Cycle : Pour le Développement des Sciences et de l'Innovation (PDSI)
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MERCI POUR VOTRE PARTICIPATION !



L'olfaction, une fonction vitale ?