

Robert Schwyzer

8 Dec 1920 – 29 Sep 2015

Professor of Molecular
Biology at the ETH Zurich
(1963 – 1988)

50 years ago

19. Die Totalsynthese des β -Corticotropins (adrenocorticotropes Hormon; ACTH)¹⁾

von R. Schwyzer²⁾ und P. Sieber

(4. X. 65)

Adrenocorticotropes Hormon aus Schweine-Hypophysen ist ein Gemisch von mindestens sieben chemisch sehr nahe miteinander verwandten Polypeptiden [2]³⁾. Die Hauptkomponente ist unzweifelhaft das β -Corticotropin (Formel I), dessen Molekel 39 Aminosäurereste umfasst und volle ACTH-Wirkung aufweist. Bei andern Spezies sind die Träger der ACTH-Wirkung fast identische Nonatriaconta-Peptide, welche sich untereinander und vom Schweine- β -Corticotropin nur im Bereiche der Aminosäuren No. 25–33 durch kleine Abweichungen in der Sequenz unterscheiden [3]. Das porcine β -Corticotropin kann deshalb, mindestens für die Zwecke der chemischen Synthese, als eine für das adrenocorticotrope Hormon (ACTH) repräsentative Molekel angesehen werden.

Die systematische Anwendung der in unserem Arbeitskreise entwickelten Methoden zur Synthese komplizierter Polypeptid-Naturstoffe (Gramicidin S [4], Angiotensin I [5] und II [6], α -melanophorenstimulierendes Hormon [7], β -melanophorenstimulierendes Hormon [8]) hat nun auch die Herstellung des β -Corticotropins (I) in Dezigramm-Mengen erlaubt. Mit seinen 39 Aminosäureresten ist dies z. Zt. der grösste und komplizierteste durch Totalsynthese in hoher Reinheit zugänglich gewordene Polypeptid-Wirkstoff.



Robert Schwyzer's happy youth in Blackduck in the northern plain of Minnesota

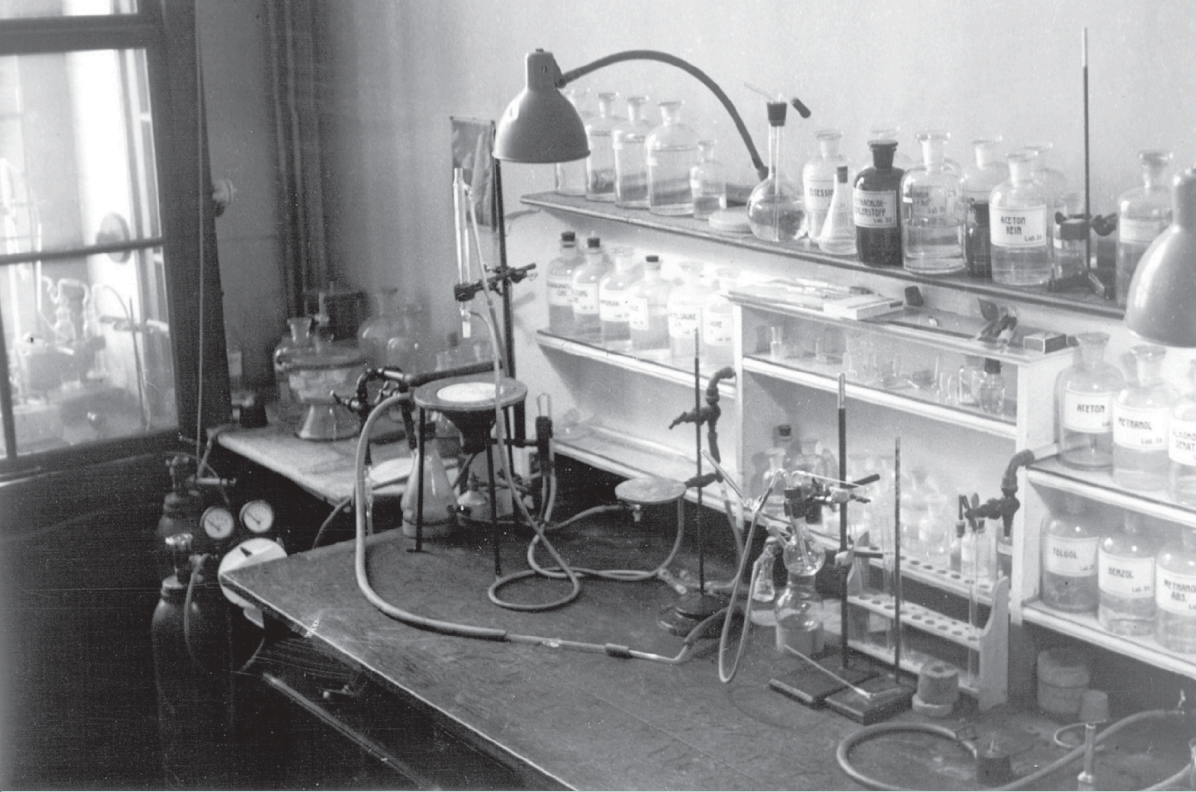
His father was a country doctor and gifted surgeon





Robert Schwyzer after the return of the family from Minnesota to Bülach / Zurich (1933): student at the grammar school in Zurich, military service during world war II (youngest lieutenant of the Swiss Army), studies of chemistry at the University of Zurich, PhD (1947) under Prof. Paul Karrer (Nobel Laureate 1937), marriage to Rosa Nägeli (1948), three children (Arnold, 1950; Regula, 1953; Hans Kaspar, 1955).





Paul Karrer

Professor of Chemistry
University of Zurich
Nobel Laureate 1937



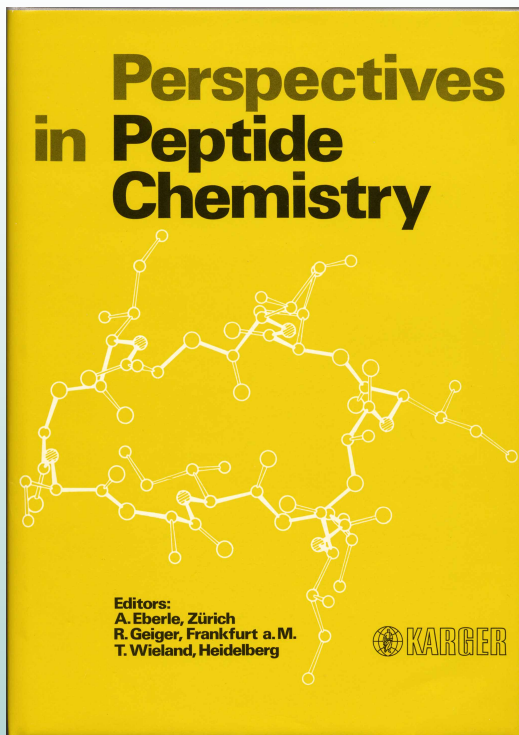
Robert Schwyzer's early research
in Paul Karrer's Institute:

Doctoral Thesis on *Vitamins and
Antivitamins* (1947)

Habilitation Thesis on *Pteridines
and Folic Acid* (1951)

Around 1950, Robert Schwyzer developed strong interests for the field of peptide chemistry and biology, but Paul Karrer thought "...that the time is not yet ripe for this..."

In 1952 Robert Schwyzer left Karrer's Institute and joined CIBA AG in Basel where he founded his first peptide group. It was to become one of the most successful and innovative pharmaceutical peptide research groups.



Book dedicated to Robert Schwyzer on the occasion of his 60th birthday (1980)

Theodor Wieland
5 Jun 1913 – 24 Nov 1995

Epochs of Peptide Chemistry

1st Epoch

1880-1915

Theodor Curtius, Emil Fischer

2nd Epoch

1920-1945

Max Bergmann, Leonidas Zervas

3rd Epoch

1945-1980

Syntheses: from Oxytocin to ACTH and Insulin

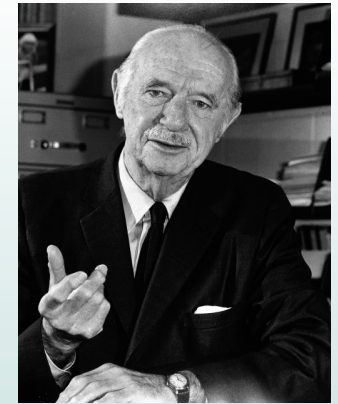
Basel's Pharmaceutical Industry took a lead into peptide chemistry in the early 1950s:

Ciba, Sandoz

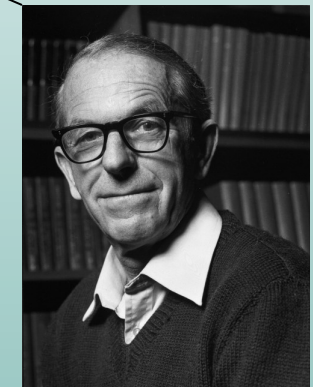
Roche, Geigy

3rd Epoch

	1953	Oxytocin: structure and synthesis
	1953/54	Vasopressin: structure and synthesis
	1955	Insulin: structure
Schwyzler, Sieber →	1956	Gramicidin S (synthesis)
Schwyzler, Rittel →	1957	[Ile ⁵]-Angiotensin II (synthesis)
Schwyzler, Kappeler →	1961	ACTH ₁₋₂₄ (synthesis)
Schwyzler <i>et al.</i> →	1963	α-MSH + β-MSH (synthesis)
Schwyzler, Sieber →	1963/65	ACTH ₁₋₃₉ (synthesis)
Meienhofer <i>et al.</i>	1963	
Kung <i>et al.</i> →	1966	Insulin (synthesis)
Katsoyannis <i>et al.</i>	1966	
Sieber <i>et al.</i> →	1974	<i>h</i> -Insulin (synthesis with specific conjugation of A and B chains)



Vincent du Vigneaud
New York (Cornell University)



Frederick Sanger
Cambridge U.K. (LMB)

*) *Nobel Prizes:* Vincent du Vigneaud (1954), Frederick Sanger (1958, 1980)

Participants of the 3rd EPS, Basel, 1960

38 Robert Schwyzer

6 Peter Sieber

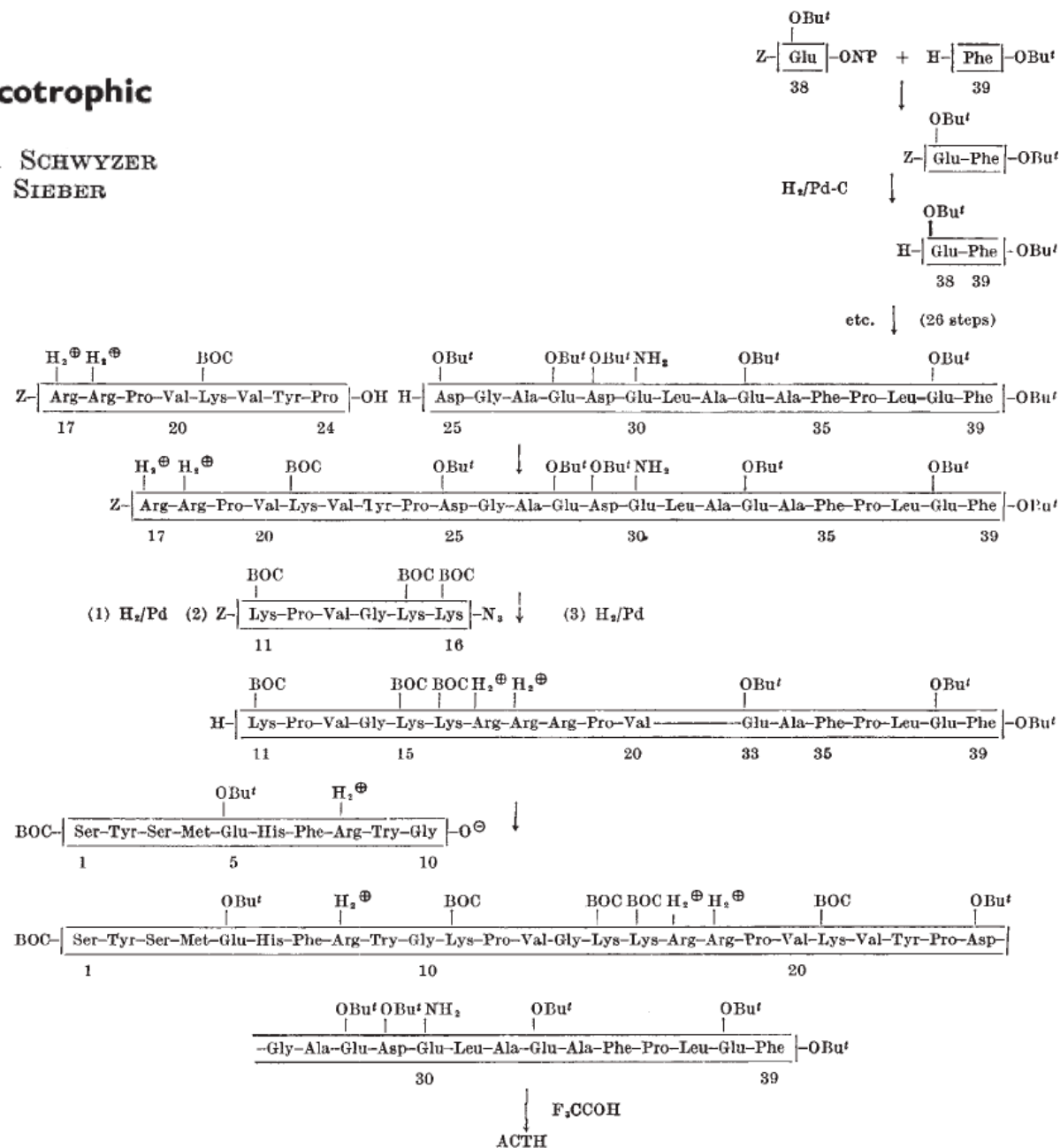
42 Max Brenner (conference organizer)

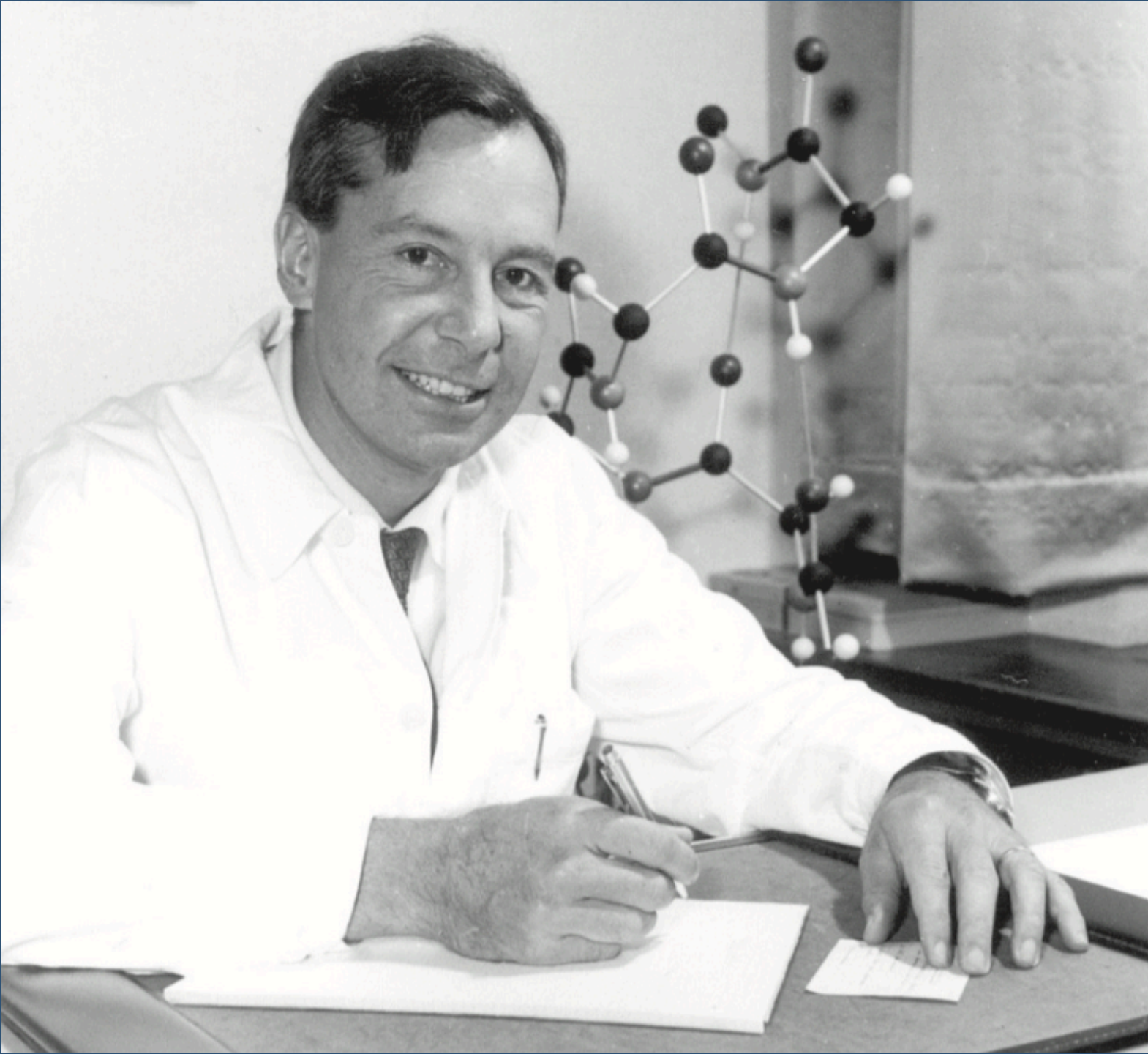


3rd European Peptide Symposium, Basel, 1960

BIOCHEMISTRY

Total Synthesis of Adrenocorticotrophic Hormone

R. SCHWYZER
P. SIEBERPharmaceutical Department,
CIBA Ltd., Basle.Fig. 2. Outline of synthesis of ACTH. Z = carbobenzyloxy; Bu^t = *t*-butyl; BOC = *t*-butoxy-carbonyl. Positions referred to in text are indicated by numerals



Offers for chairs from abroad, e.g. from the University of Washington (Department of Biochemistry) Seattle

The **ETH in Zurich**, however, offered Robert Schwyzer an even more prestigious chair: to become the founding head of a new institute, the **Institute of Molecular Biology and Biophysics**, located in a new building as part of the new ETH site on Zurich-Hönggerberg (1963)



Institutes of Molecular Biology

ETH Zurich: Research on peptides and proteins

R. Schwyzer, H. Zuber, J. Rudinger, K. Wüthrich

University of Zurich: Research on RNA and DNA

C. Weissmann, M. Billeter

1950/60s

1980s



Robert Schwyzer

Example

1963/65: chemical synthesis of ACTH

Message-address concept

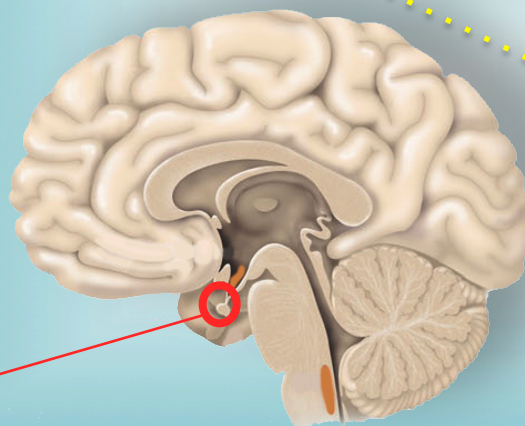
Targeting of radiopeptides

Multivalent peptide constructs

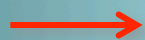
Virus as carrier for peptides

Peptide-receptor interactions

Peptide-membrane interactions



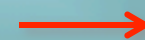
ACTH
 α -MSH
 β -MSH



Many species

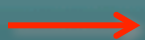


Radiopeptides

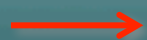


Struct. analogs

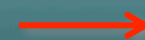
β -Lipotropin
 β -Endorphin
CLIP
 γ -MSH



Many species



Radiopeptides



Struct. analogs

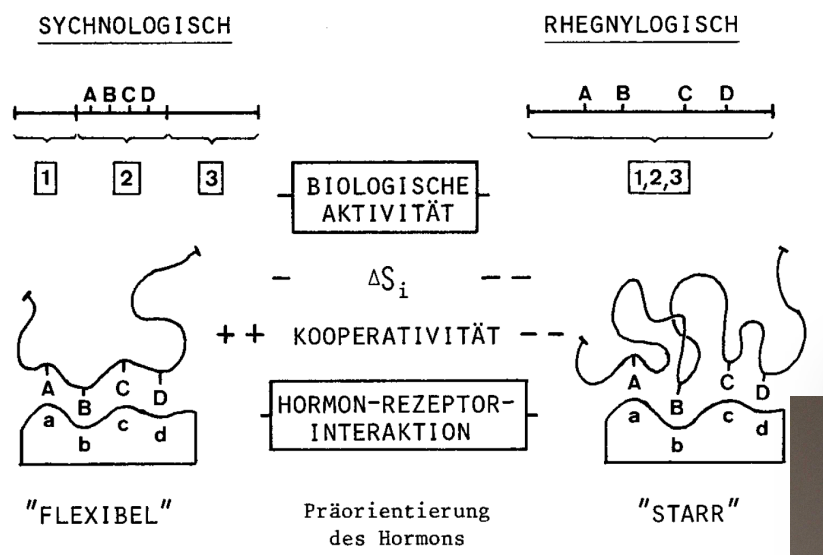
Isolation,
Sequencing

Immunoassays
Receptor assays

SAR studies
Receptor studies

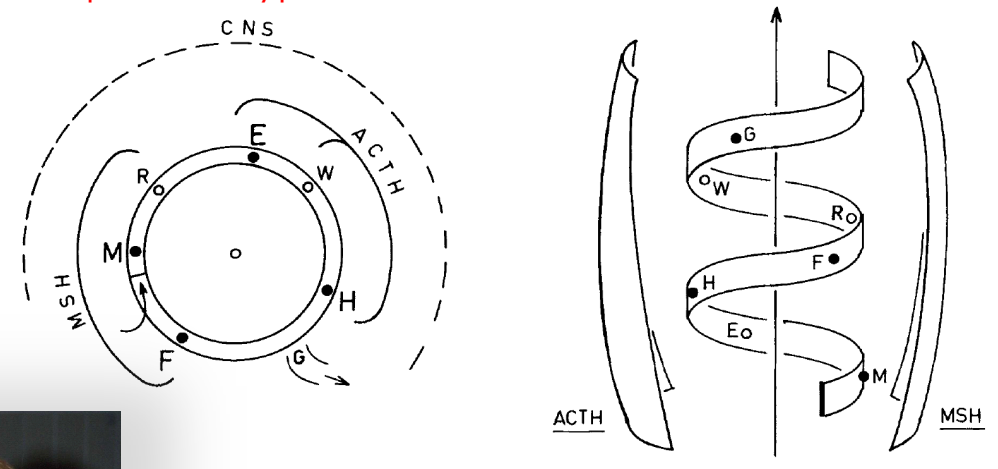
1973

ORGANISATION DER INFORMATION

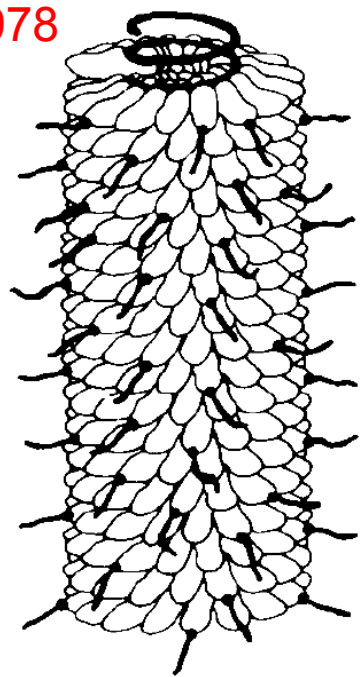


Differential recognition of peptides by receptor subtypes

1977



1978

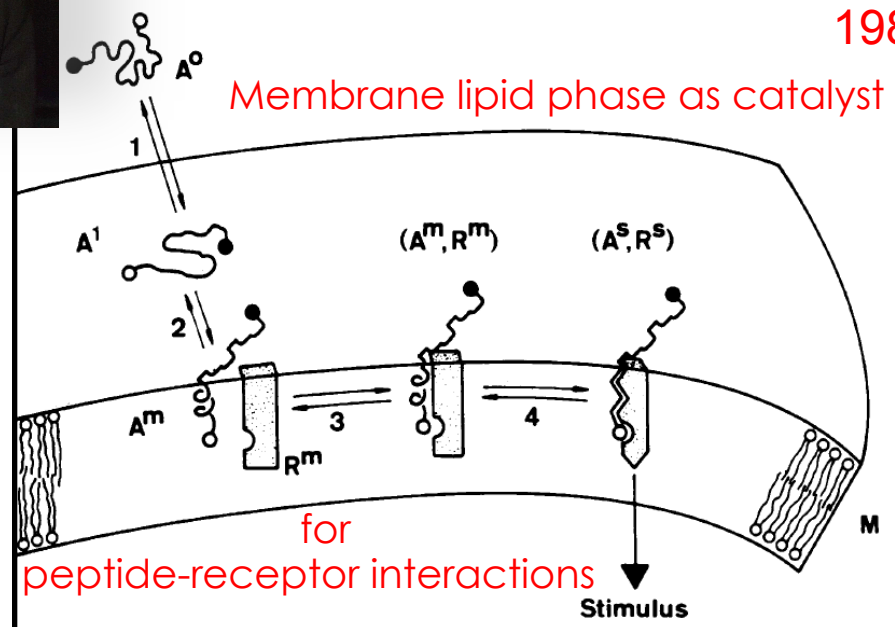


Robert Schwyzer, pioneer of nanobody-peptide constructs

TMV as nanobody carrier for biologically active peptides

- ◆ Superpotency
- ◆ Increased affinity
- ◆ Prolonged action

1986





Robert Schwyzer was a gifted lecturer and he was a talented pioneer at the interface of (peptide) chemistry and biology, initiating numerous methods and concepts that had an impact until these days.

Robert Schwyzer will be remembered as one of the most outstanding peptide scientists of the 3rd epoch.



PEPTIDE RESEARCH AT THE INTERFACE OF CHEMISTRY AND BIOLOGY

Symposium in Honour of Robert Schwyzer's 80th Birthday, 23rd Nov 2000, Bachem Inc, Bubendorf



Fritz Daniel Jakob Rosa Jean-P. Peter Günther Robert Beat Peter Alex
Dick Erne Nüesch Schwyzer Durieux Grogg Jung Schwyzer Ernst Schiller Eberle

QOHELET / KOHELET
(King James Version)

To every thing there is a season, and a time to every purpose under the heaven:

A time to be born, and a time to die;
a time to plant, and a time to pluck up
that which is planted;

A time to kill, and a time to heal; a time
to break down, and a time to build up;

A time to weep, and a time to laugh;
a time to mourn, and a time to dance;

A time to cast away stones, and a time
to gather stones together; a time to
embrace, and a time to refrain from
embracing;

A time to get, and a time to lose; a
time to keep, and a time to cast away;

A time to rend, and a time to sew; a
time to keep silence, and a time to
speak;

A time to love, and a time to hate; a
time of war, and a time of peace...



Robert Schwyzer
† 29 September 2015