VITAMIN D:

Mechanism of Action
Status of the Evidence

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Disclosure

I have no financial interest to disclose with regard to this presentation.

Objectives

- Identify at least 5 vitamin D sensitive diseases
- Identify 2 major differences between nutrients and drugs

CHRONIC DISEASES

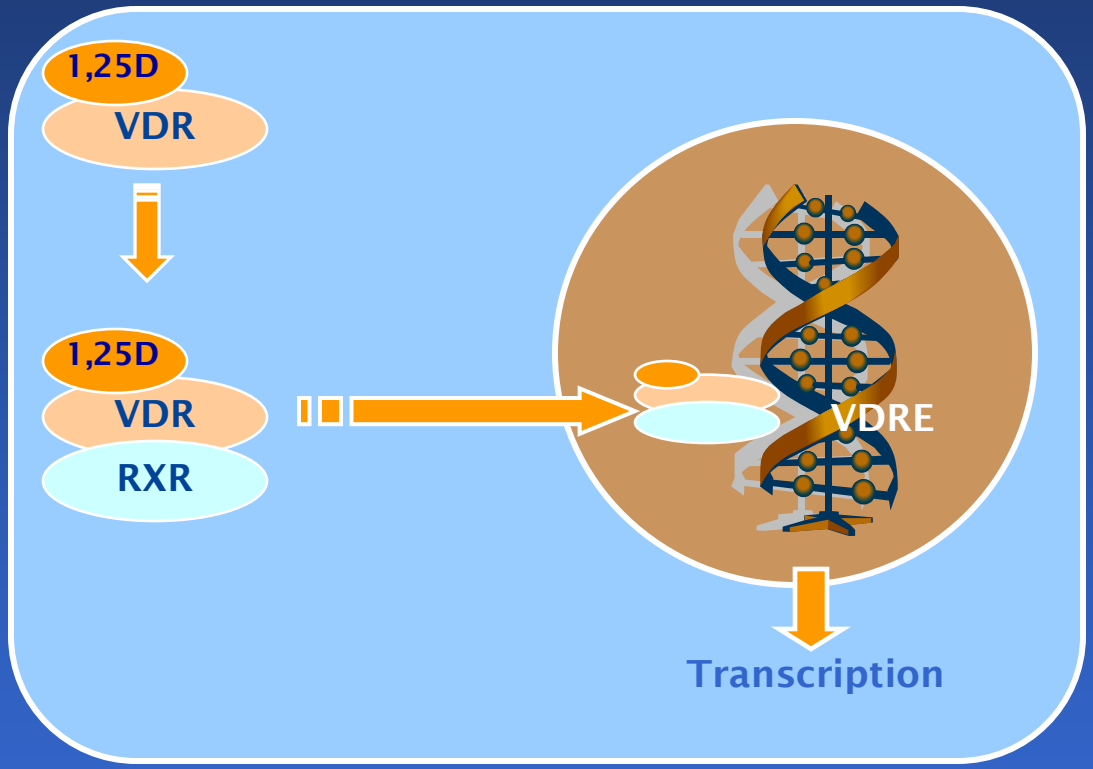
Disease	Status of Evidence
osteoporosis	++++
osteoarthritis	+
falls/neuromusc. fcn	++++
multiple sclerosis	++
fibromyalgia-like syndrome	++
type I diabetes	++
insulin sensitivity	++
cardiovascular disease	+++
pregnancy outcomes	++++
periodontal disease	++++
various cancers	++++
tuberculosis	++++
hypertension	++++

A question:

how can a single nutrient act in so many different systems and tissues?

AUTOCRINE ACTION

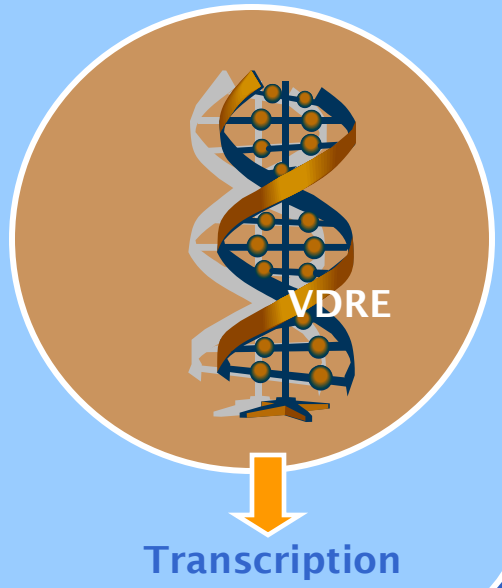
- 25(OH) D



AUTOCRINE ACTION

- 25(OH) D

- cell proliferation
- cell differentiation
- apoptosis
- immune response
- 24-hydroxylase



AUTOCRINE ACTION

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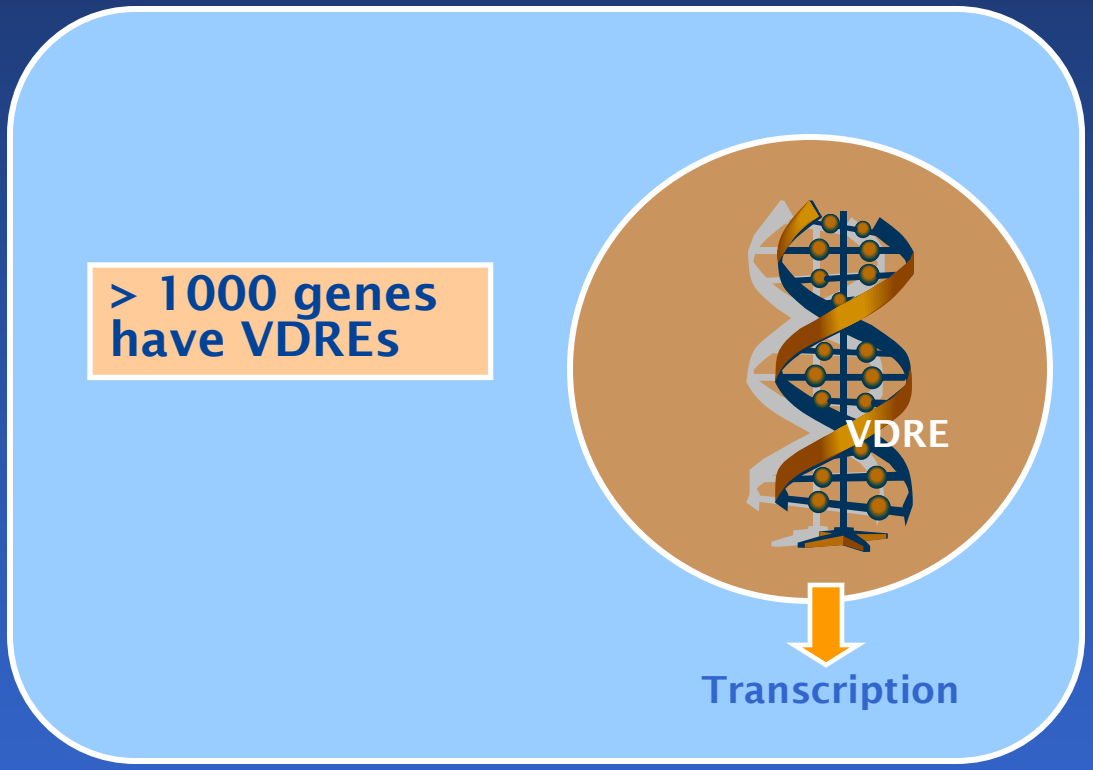

AUTOCRINE ACTION

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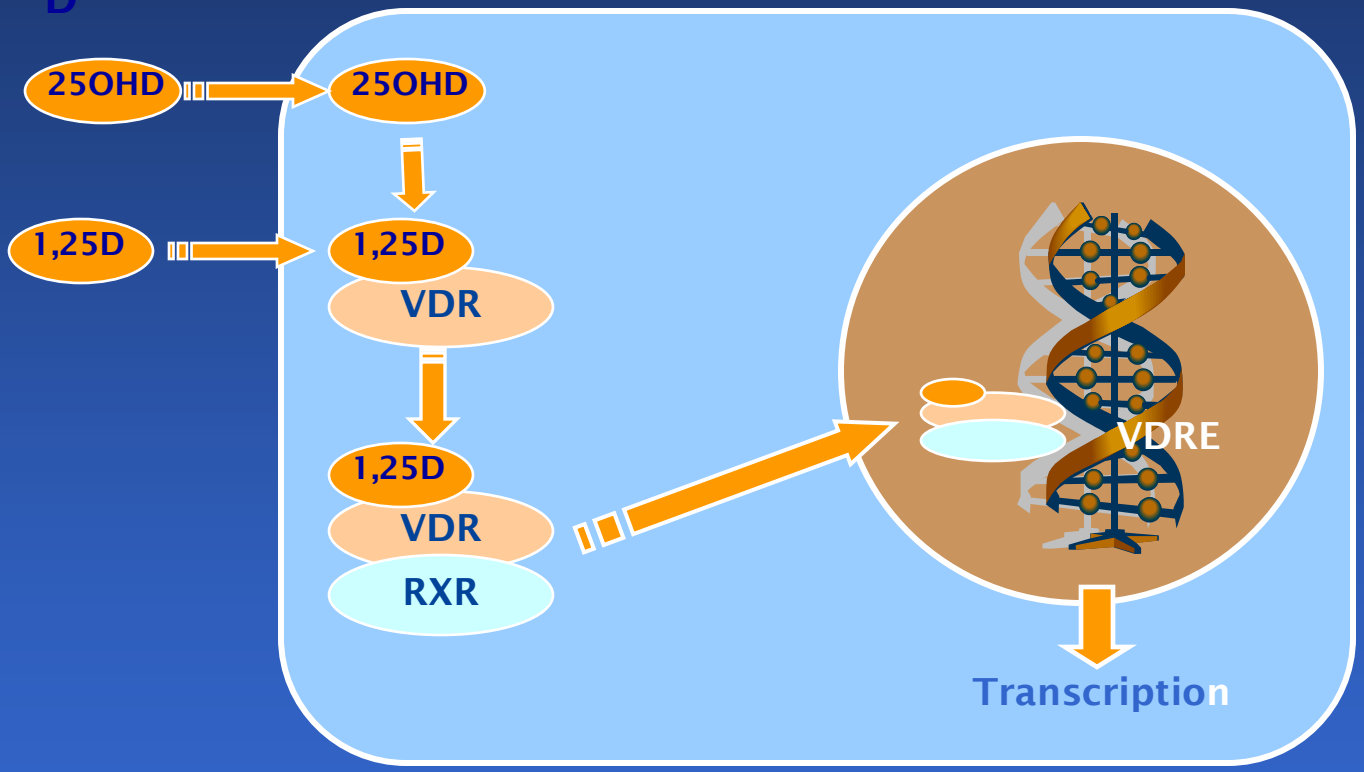

AUTOCRINE ACTION

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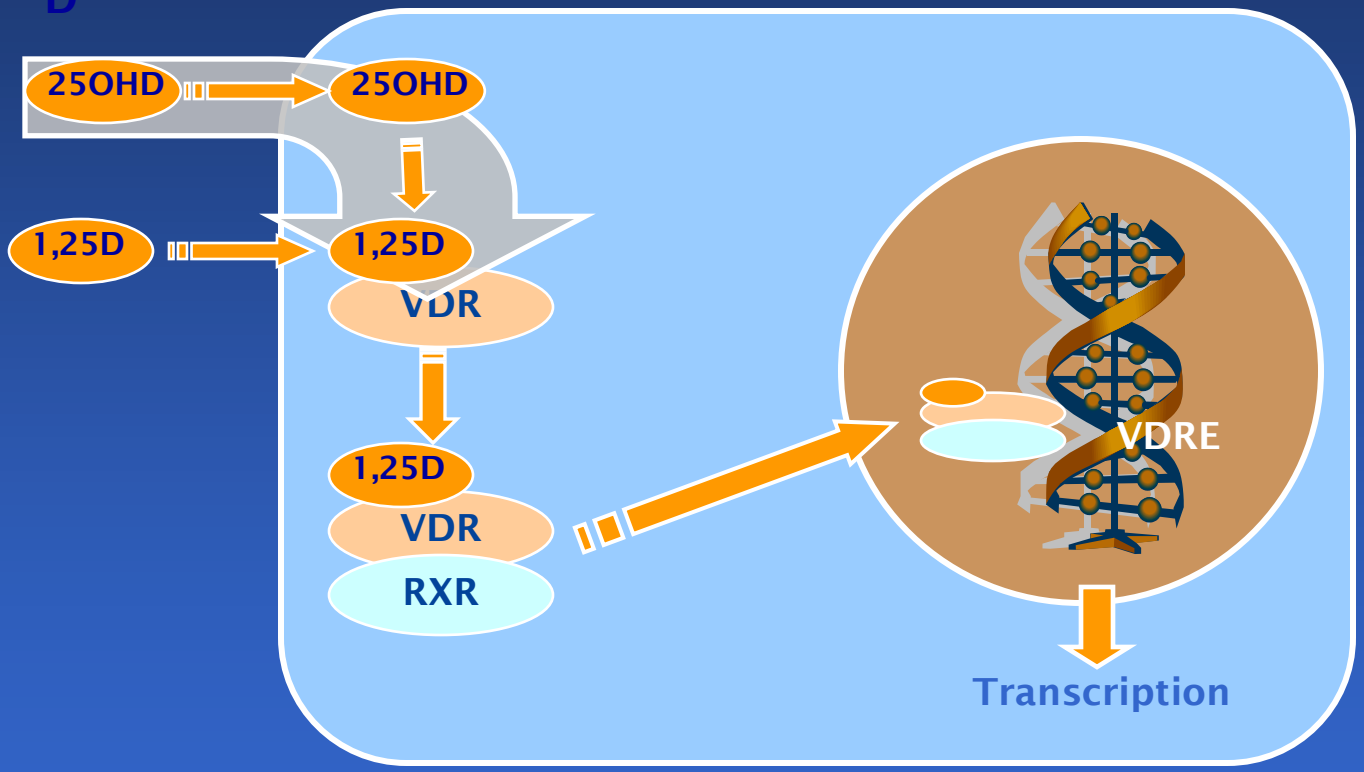
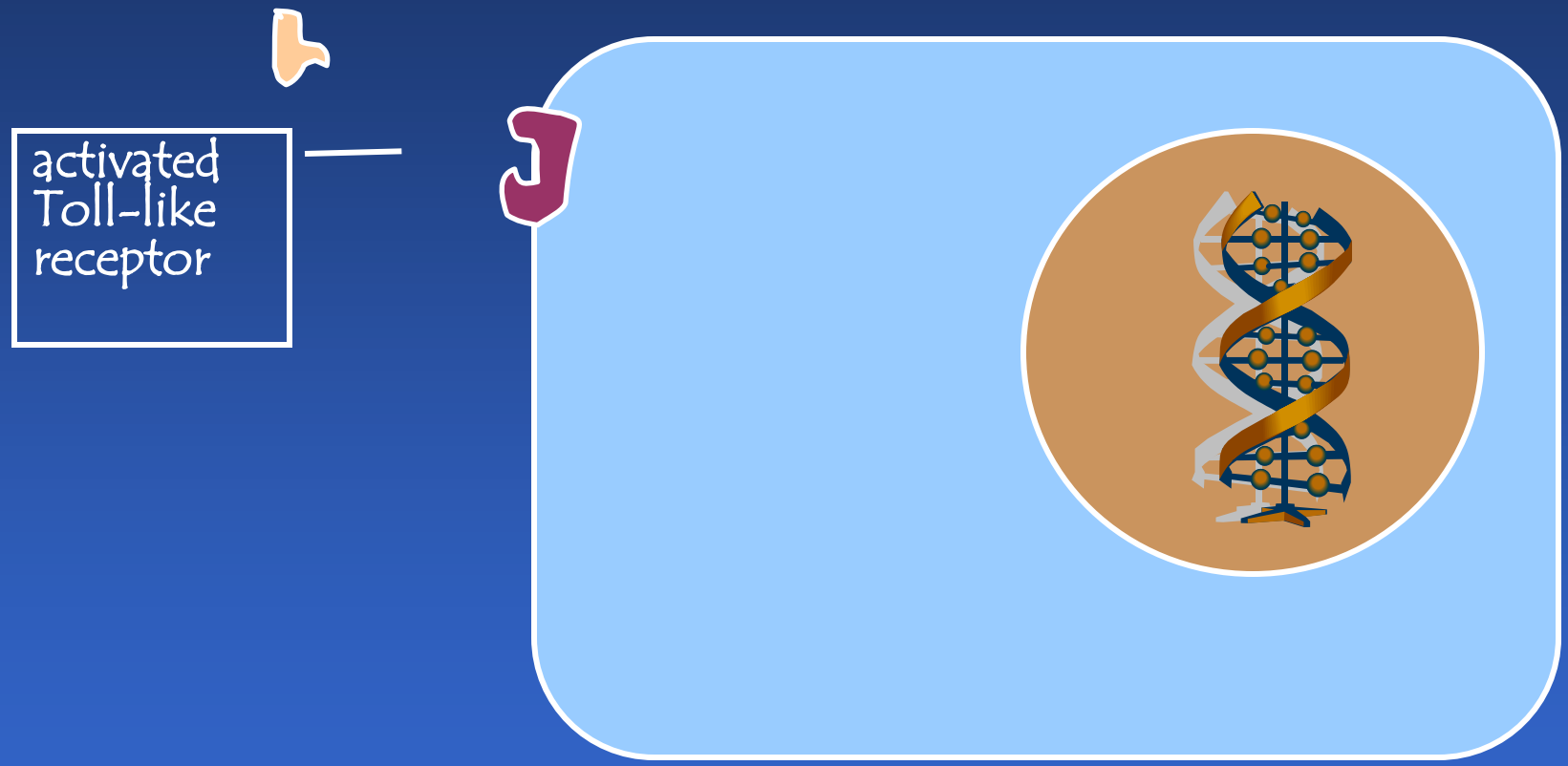


This scheme means that each tissue

- has the amount of $1,25(OH)_2D$ it needs
- when it needs it
- and is not dependent upon a "one-size-fits all" systemic level of circulating $1,25(OH)_2D$

VITAMIN D & INNATE IMMUNITY*



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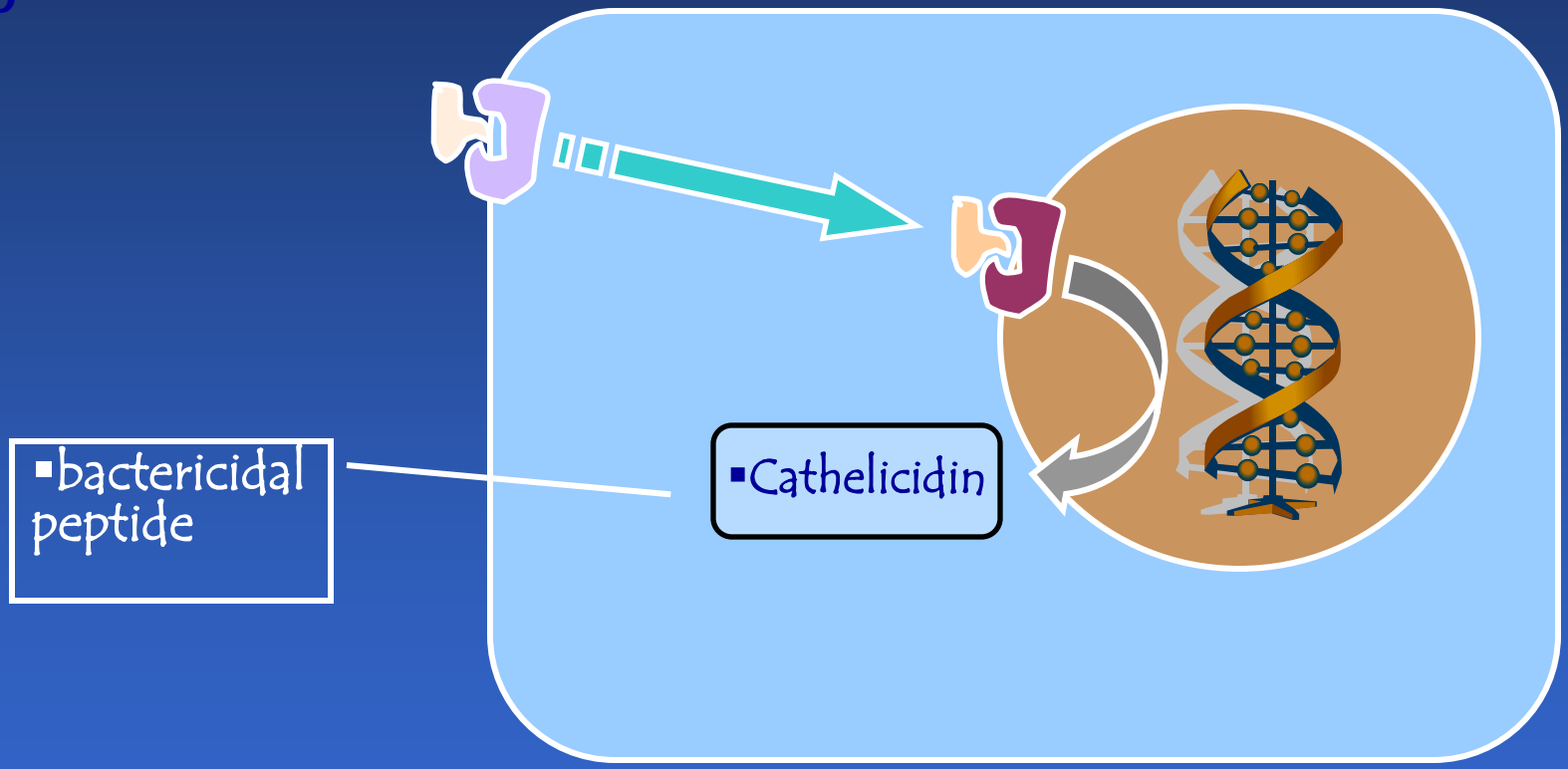
*Liu et al., Science 2006

VITAMIN D & INNATE IMMUNITY*

- 25(OH) D



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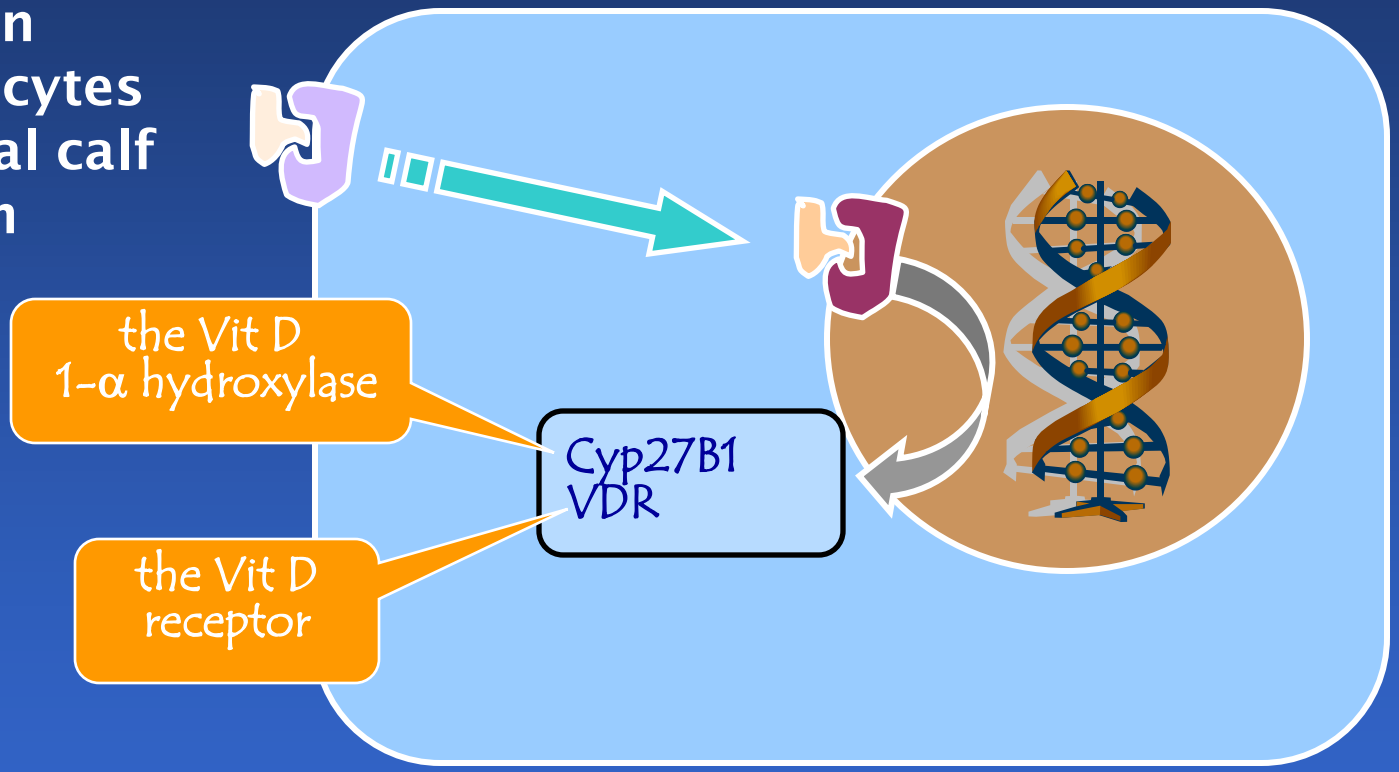
- *Liu et al., Science 2006

VITAMIN D & INNATE IMMUNITY*

- 25(OH)D human monocytes in fetal calf serum



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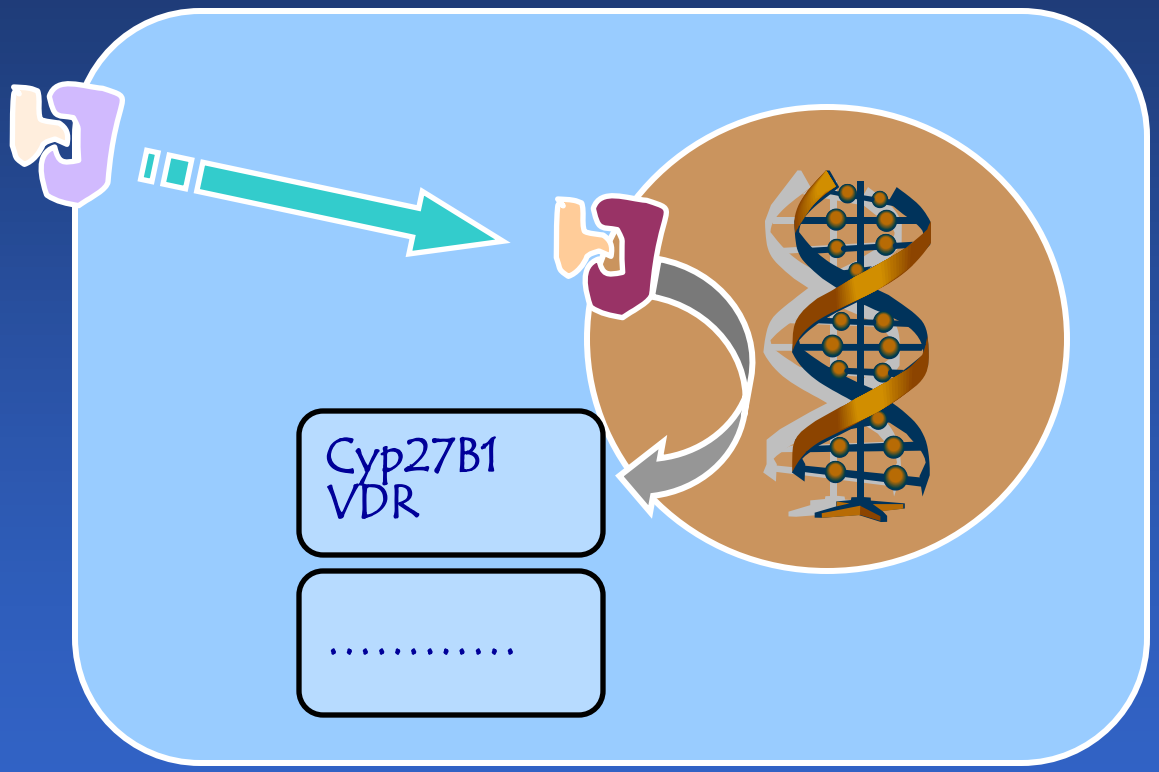
- *Liu et al., Science 2006

VITAMIN D & INNATE IMMUNITY*

- 25(OH)D human monocytes in fetal calf serum
- fetal calf serum is low in both 25(OH)D & $1,25(OH)_2D$



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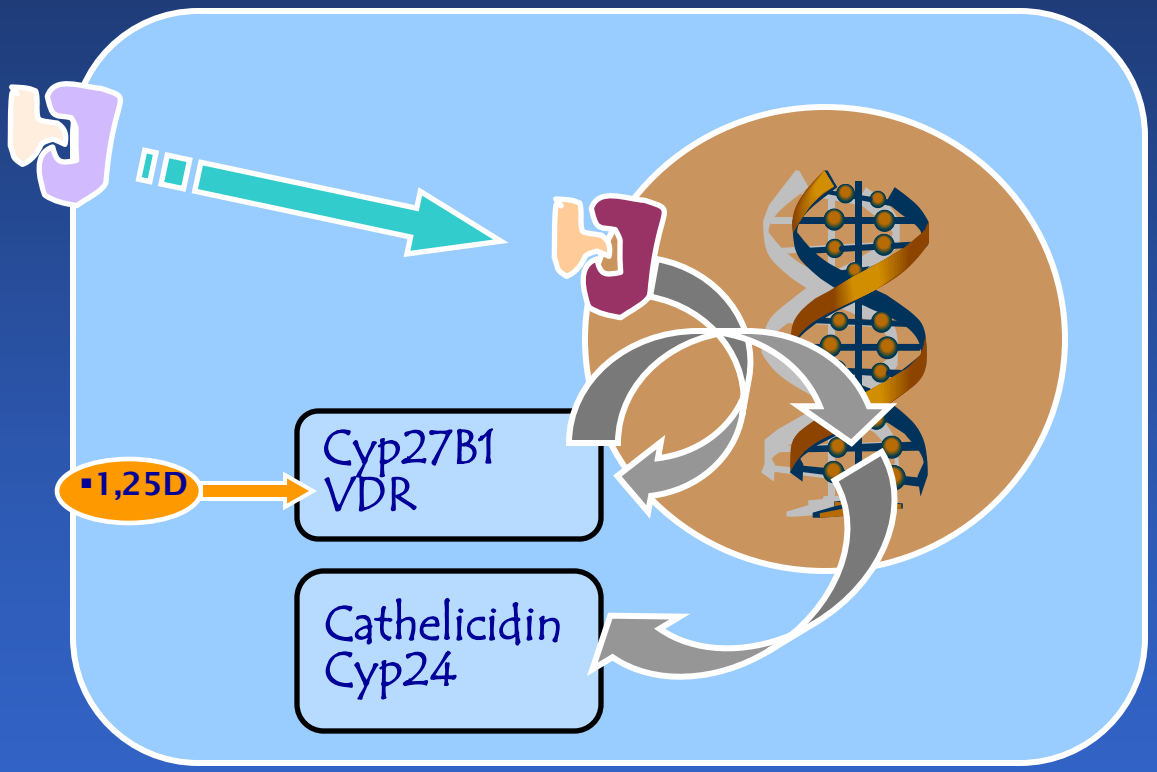
*Liu et al., Science 2006

VITAMIN D & INNATE IMMUNITY*

- 25(OH)D human monocytes in fetal calf serum
- add $1,25(OH)_2D$ to the system



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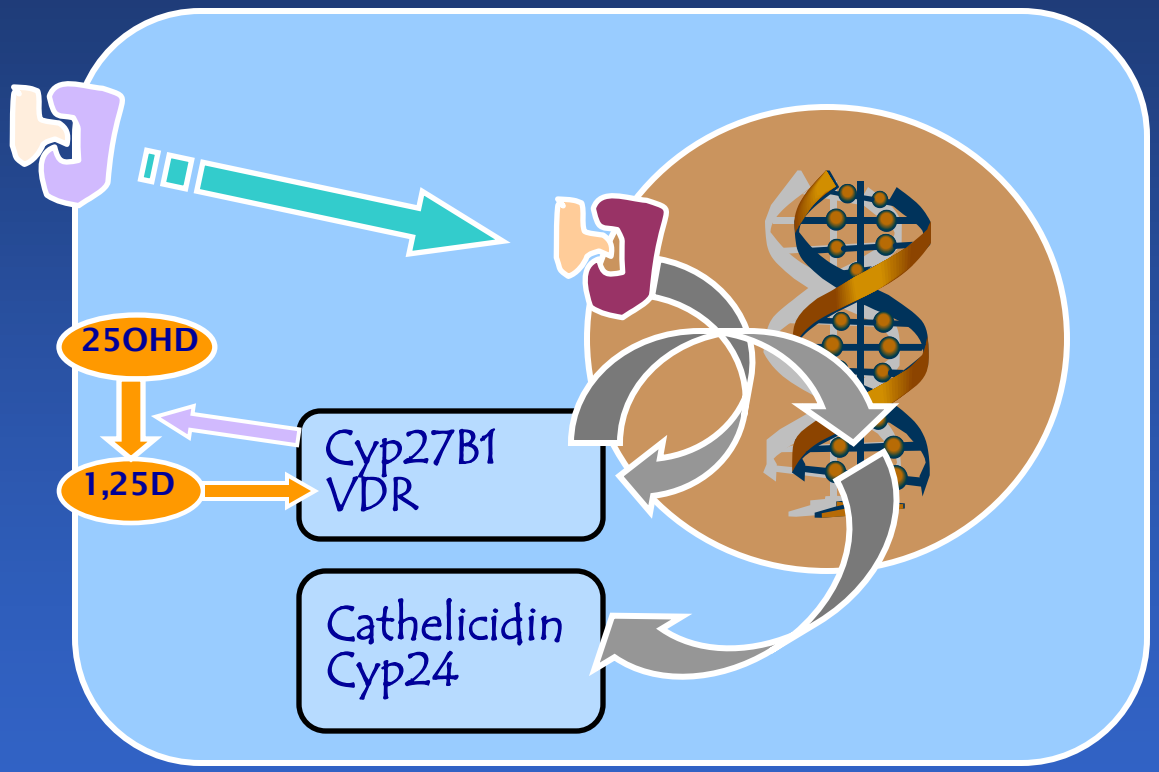
- add 25(OH) D to the system



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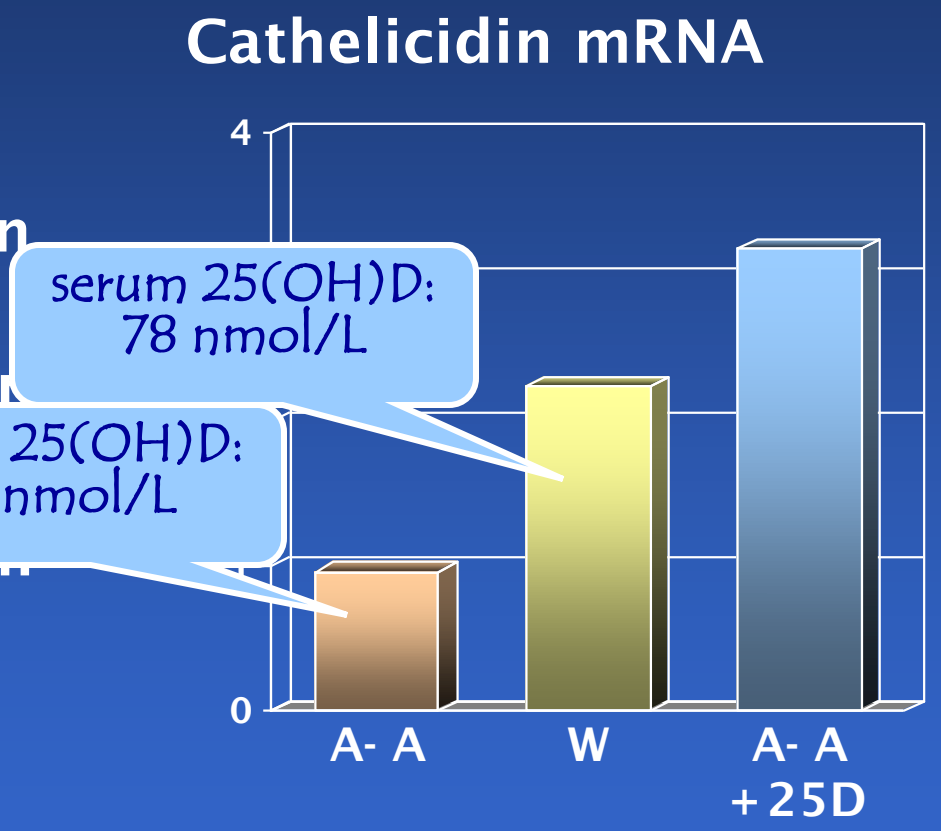
*Liu et al., Science 2006

VITAMIN D & TUBERCULOSIS

- human monocytes activated with *M. Tuberculosis* and incubated in human serum
  - African-American
  - White
  - African-American with added 25(OH)D



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*Liu et al., Science 2006

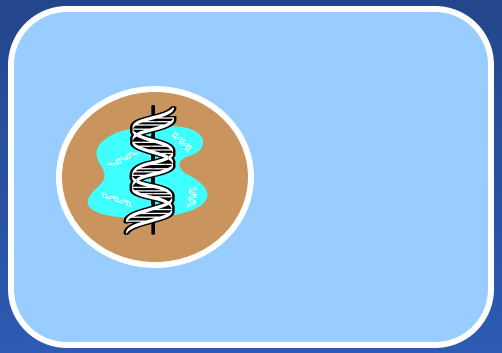
VITAMIN D & TUBERCULOSIS

these experiments show that:

- vit D is an essential mediator in the innate immune response
- serum 25(OH)D is the critical variable
- at least some of the increased sensitivity to infection in vit D-deficiency is due to reduction in response to infectious agents because 25(OH)D is rate-limiting
- the greater tuberculosis susceptibility of blacks is due in part to their low vit D status

CELL MODELS

old:

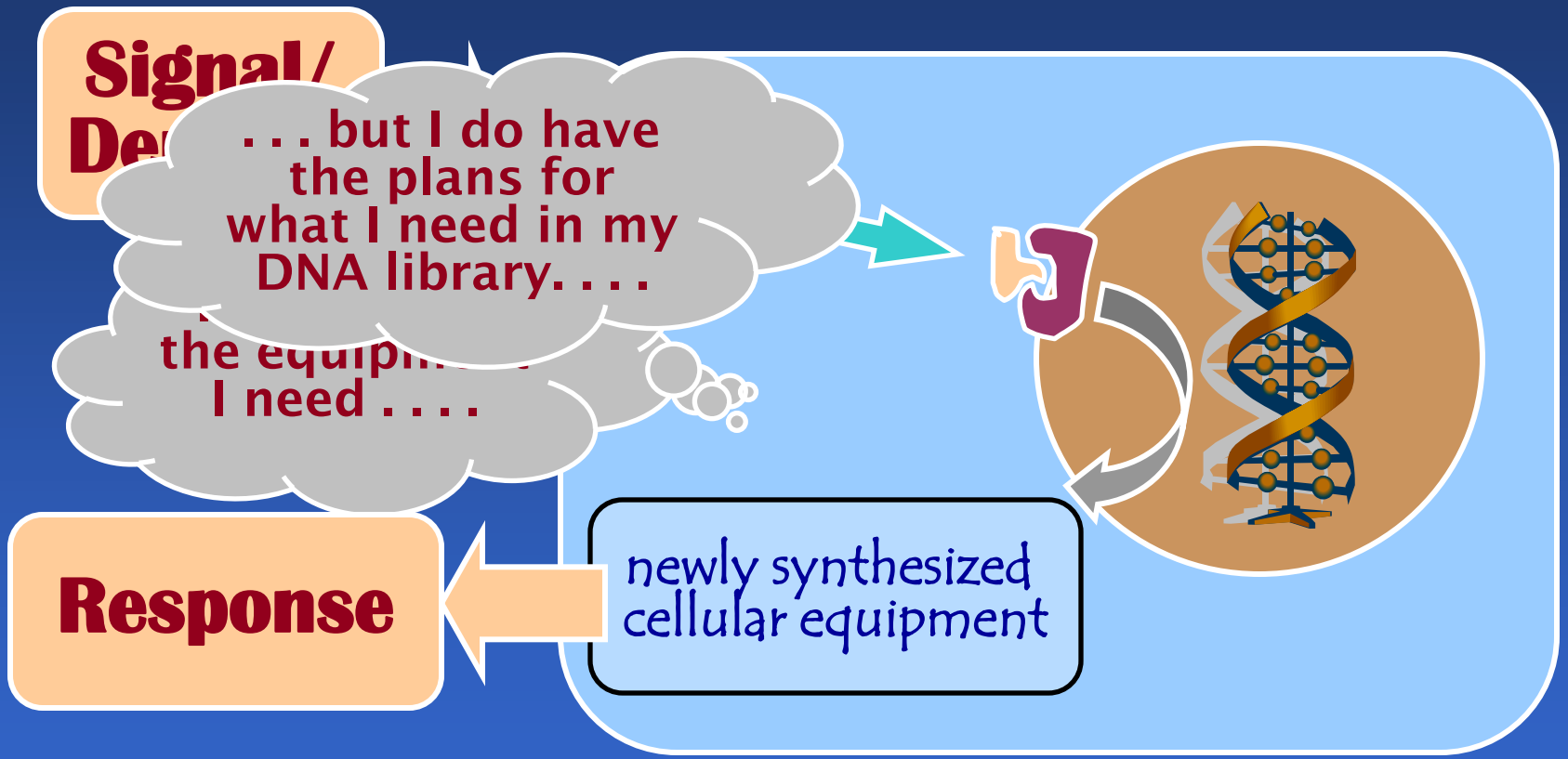


- DNA in somatic cells functions mainly to make faithful copies for tissue repair or replacement

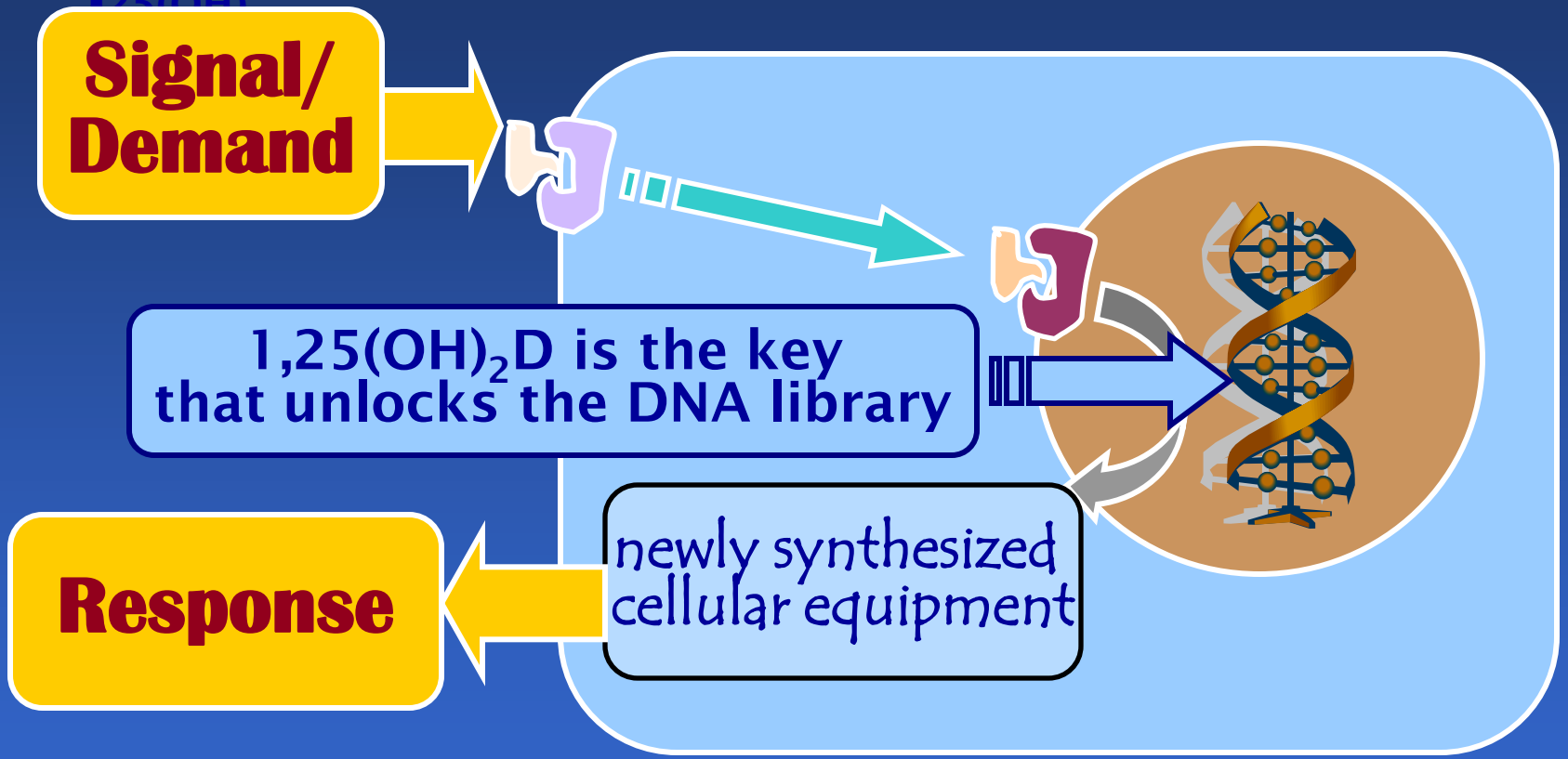
new:

- DNA functions constantly in synthesis of needed cellular apparatus

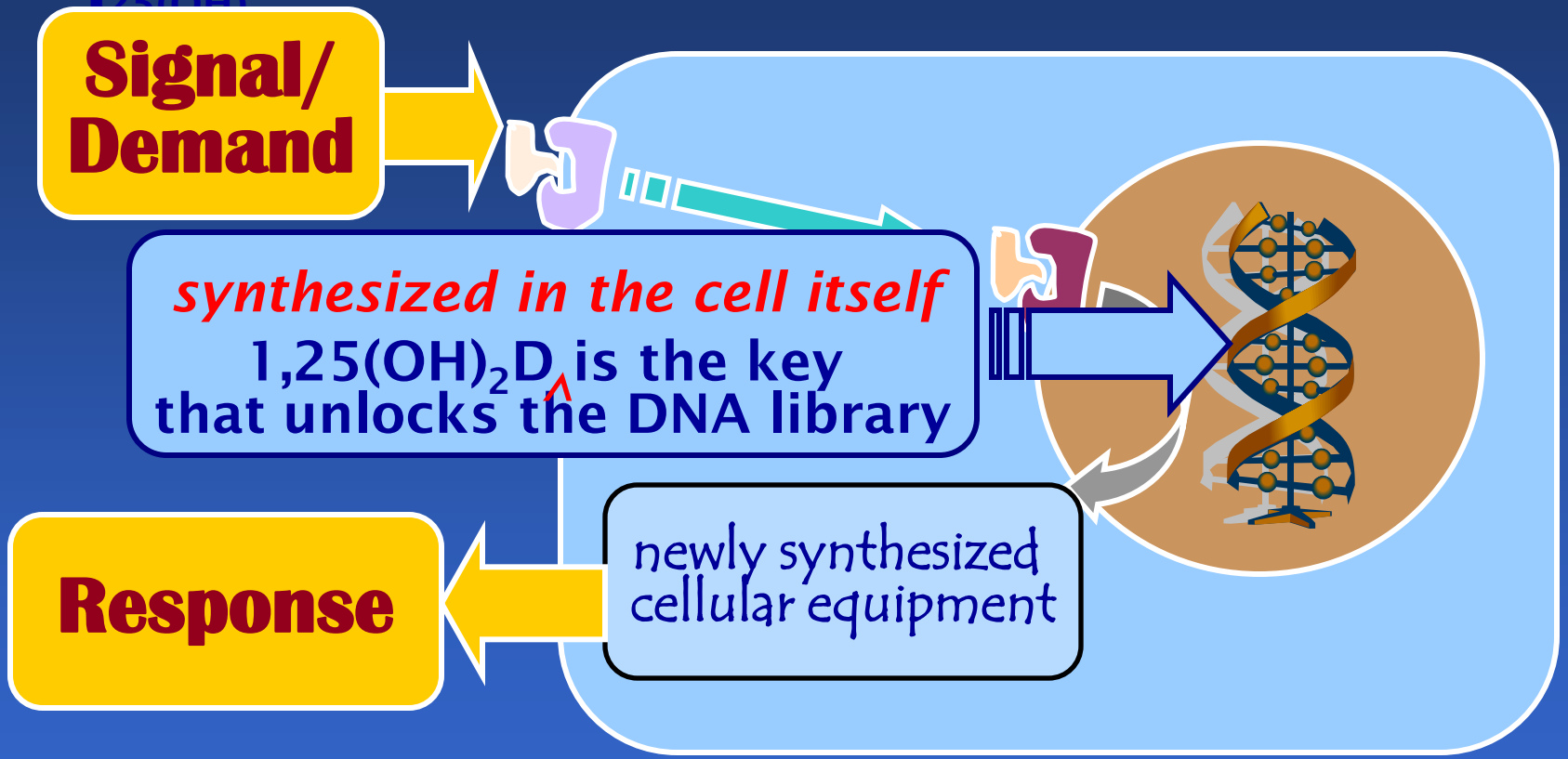
HOW A CELL RESPONDS



HOW A CELL RESPONDS



HOW A CELL RESPONDS



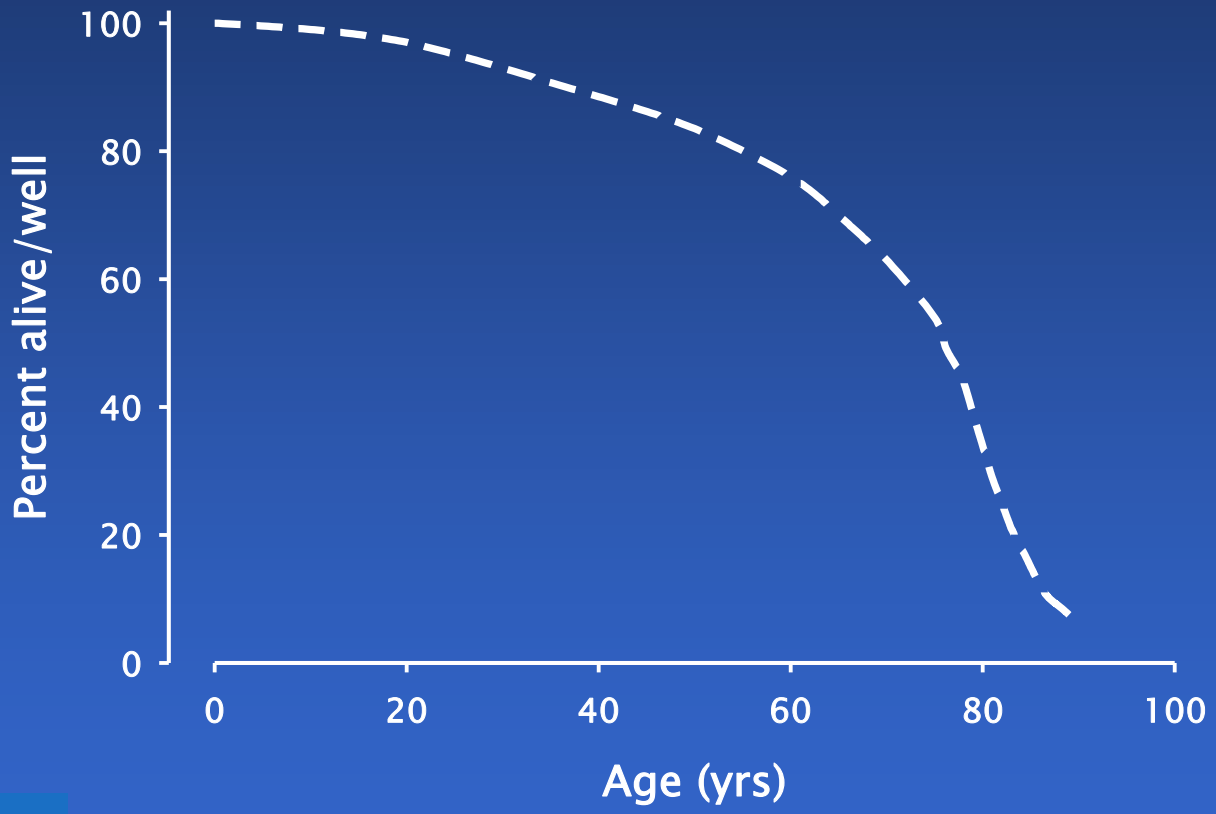
VITAMIN D SHORTAGE

- when vitamin D is in short supply, the various tissues and cells of our bodies cannot make enough calcitriol to open up their DNA libraries adequately
- their functioning is thus impaired

WHAT ARE THE CONSEQUENCES?

- bone diseases, falls, & fractures
- hypertension
- ↑ risk of cardiac disease & death
- prematurity, low birth weight, & ↑ Caesareans
- diabetes & metabolic syndrome
- periodontal disease
- decreased resistance to infection
- various cancers
- ↑ risk of multiple sclerosis

SQUARING THE MORTALITY CURVE



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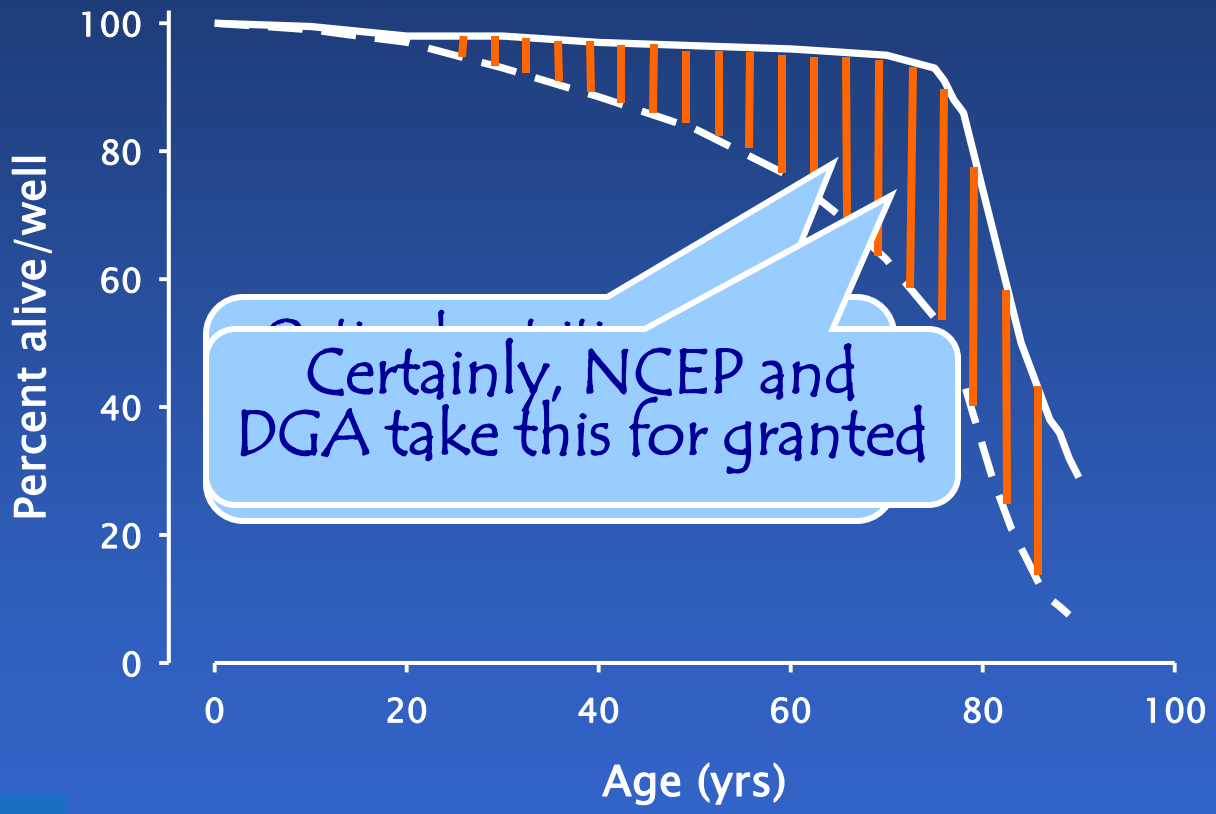
SQUARING THE MORBIDITY CURVE



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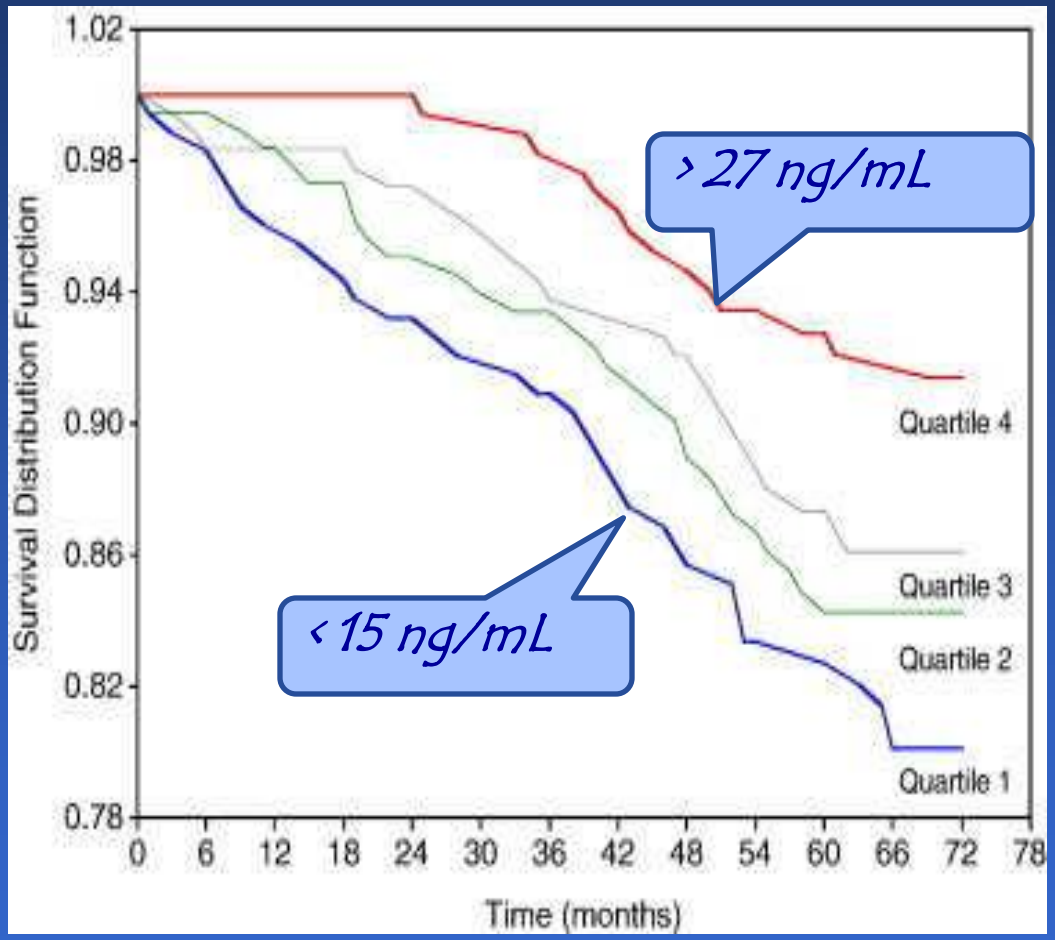
ALL-CAUSE MORTALITY*

- 714 community dwelling women
- aged 70–79
- Baltimore Women's Health & Aging Studies I & II
- median follow-up: 72 months
- risk adjusted for age, race, BMI, & other factors associated with mortality
- hazard ratio (Q4 vs. Q1): 2.45 (CI: 1.1–5.4; P< 0.02)



* Semba et al. (2009) Nutr Res 29:525–530

STATUS OF THE EVIDENCE

- there are now more than 30 randomized controlled trials evaluating a causal connection between serum 25(OH)D levels and various health benefits
  - 13+ osteoporotic fractures
  - 5+ falls
  - 2 hypertension
  - 1 cancer
  - 1 adjuvant tuberculosis therapy
  - 3 respiratory infection/influenza risk
  - 1 pregnancy outcomes
  - 1 periodontal disease
  - 3 insulin sensitivity & diabetes

STATUS OF THE EVIDENCE

- out of this total there are, to be sure, several null trials
- in general these failed trials either –
  - used too low a dose
  - had poor compliance
  - failed to achieve a therapeutic blood level of 25(OH)D
  - failed to optimize co-nutrition
- there are *no* negative trials

STATUS OF THE EVIDENCE

- there are, to be sure, several null trials as well
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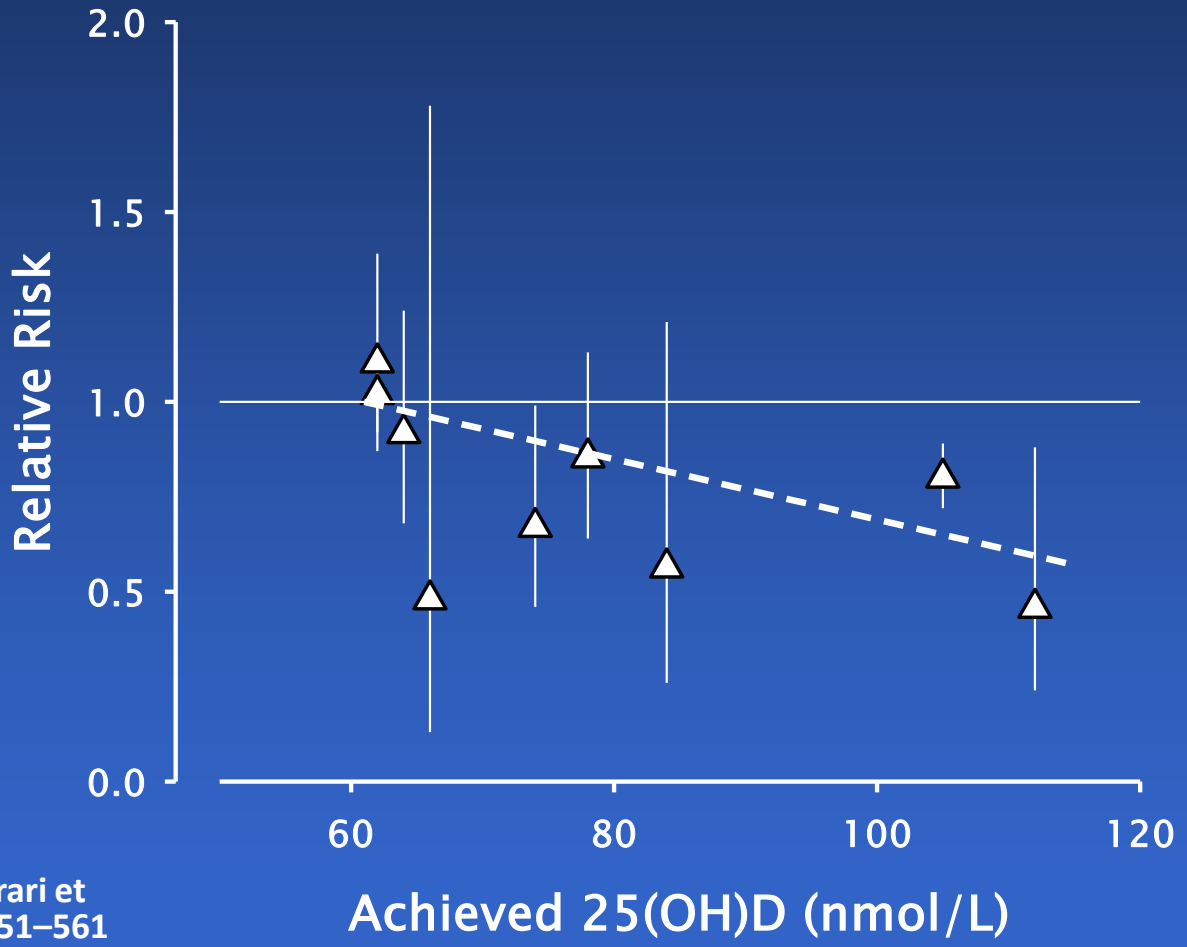
ACHIEVED DOSE & EFFICACY*



* Redrawn from Bischoff-Ferrari et al. (2009) Arch Int Med; 169:551–561

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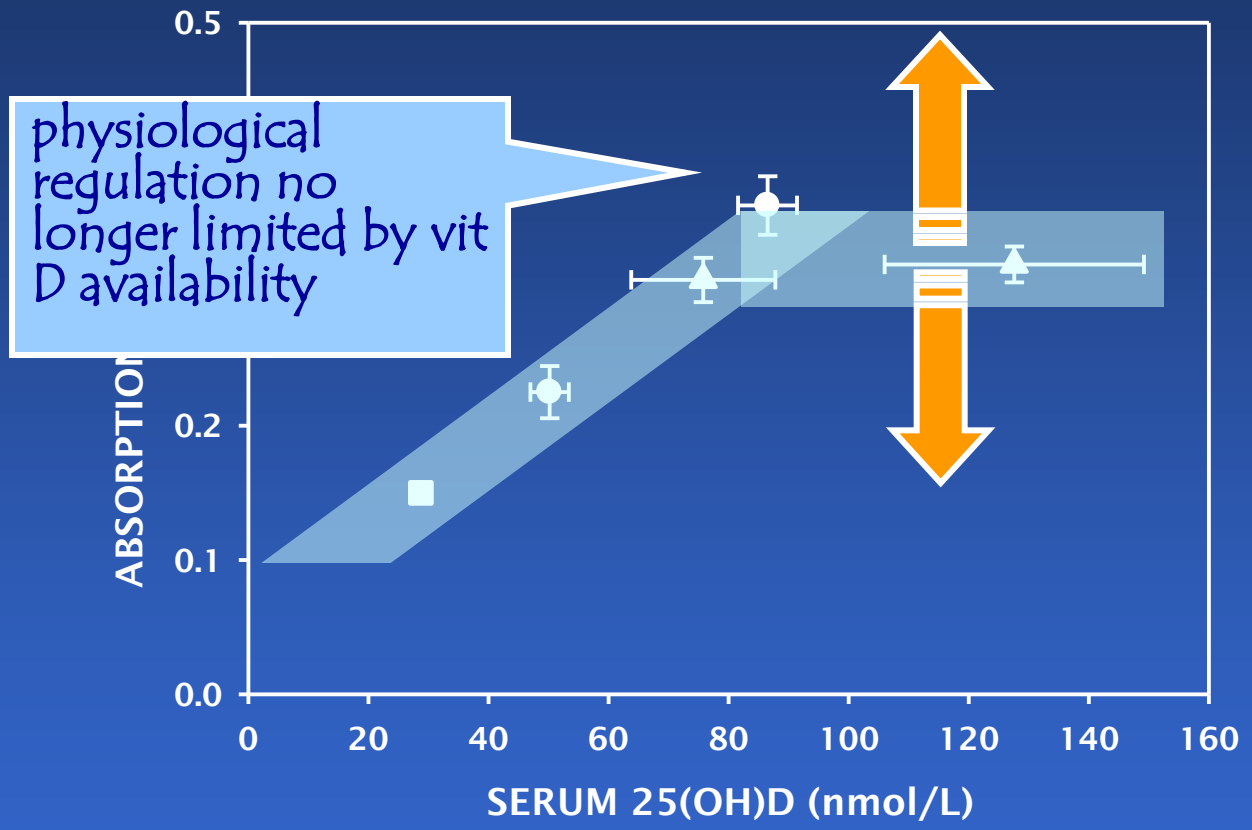
A VITAMIN D THRESHOLD



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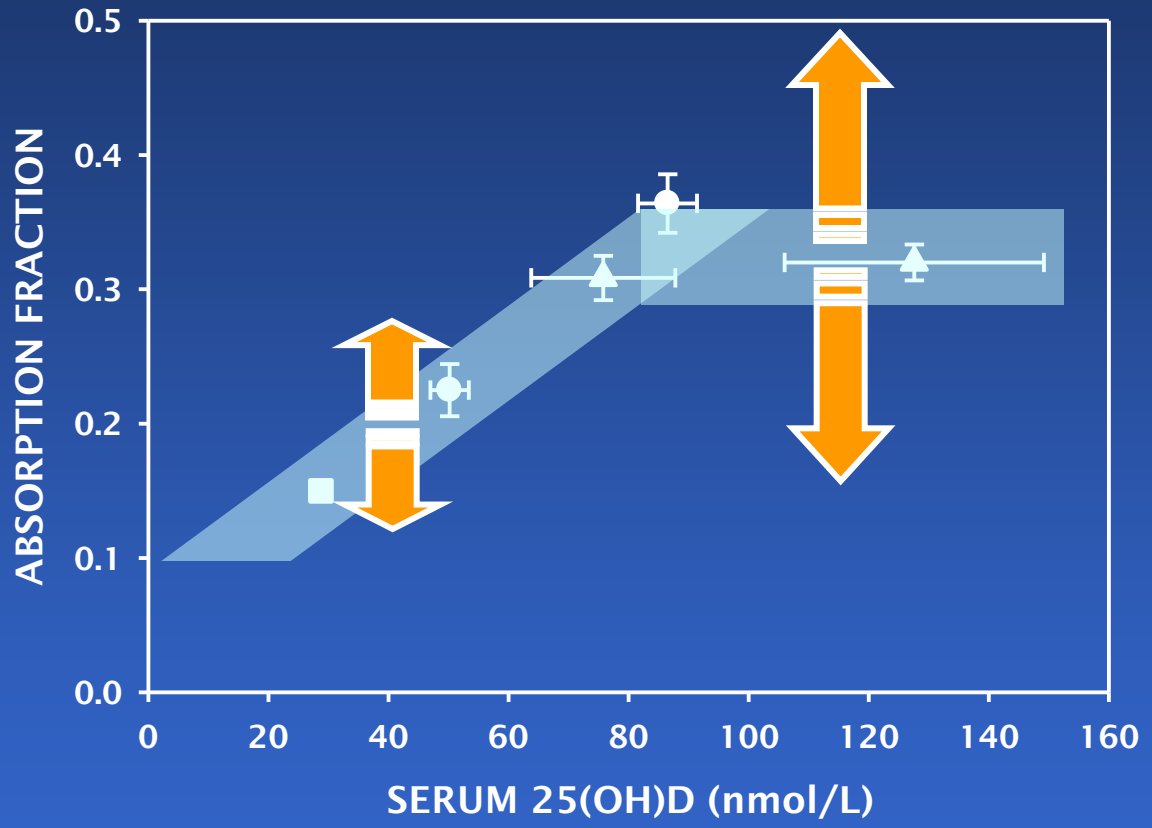

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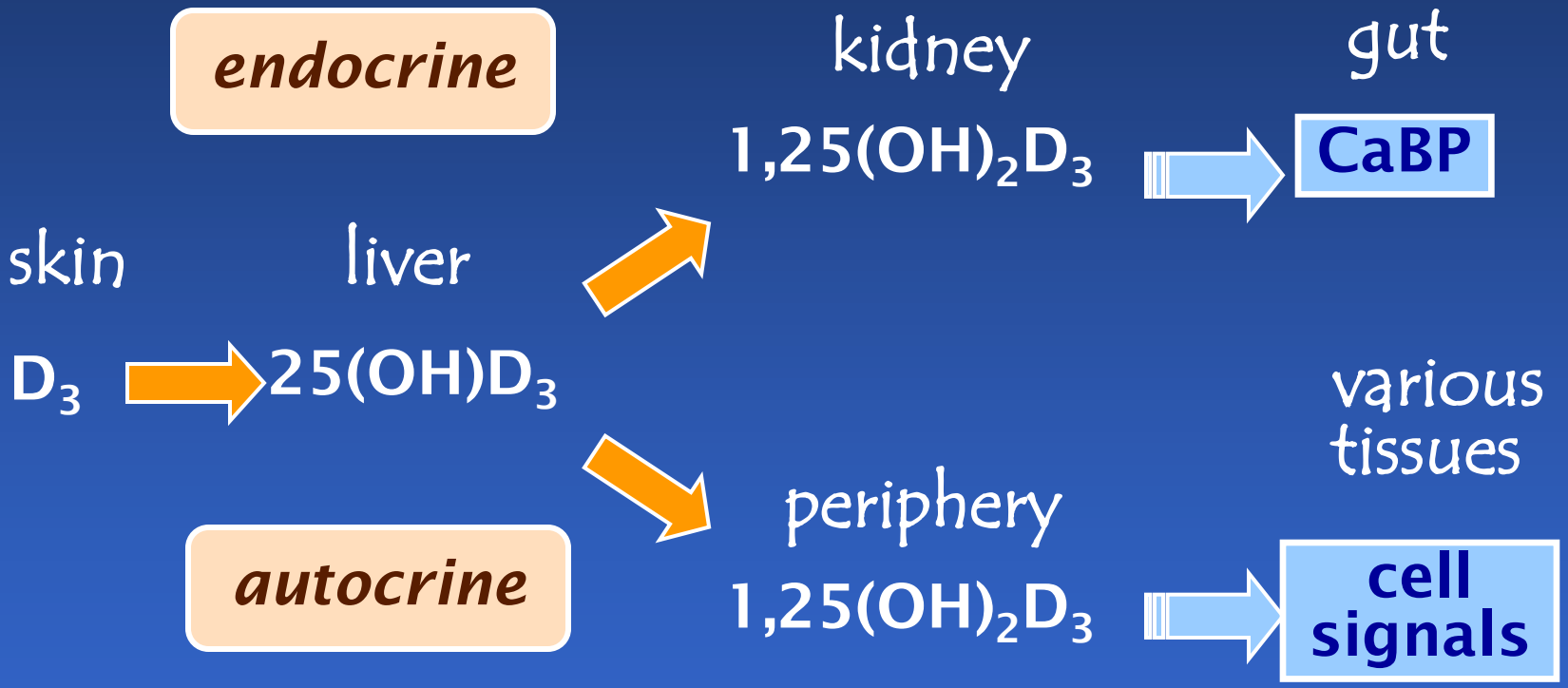
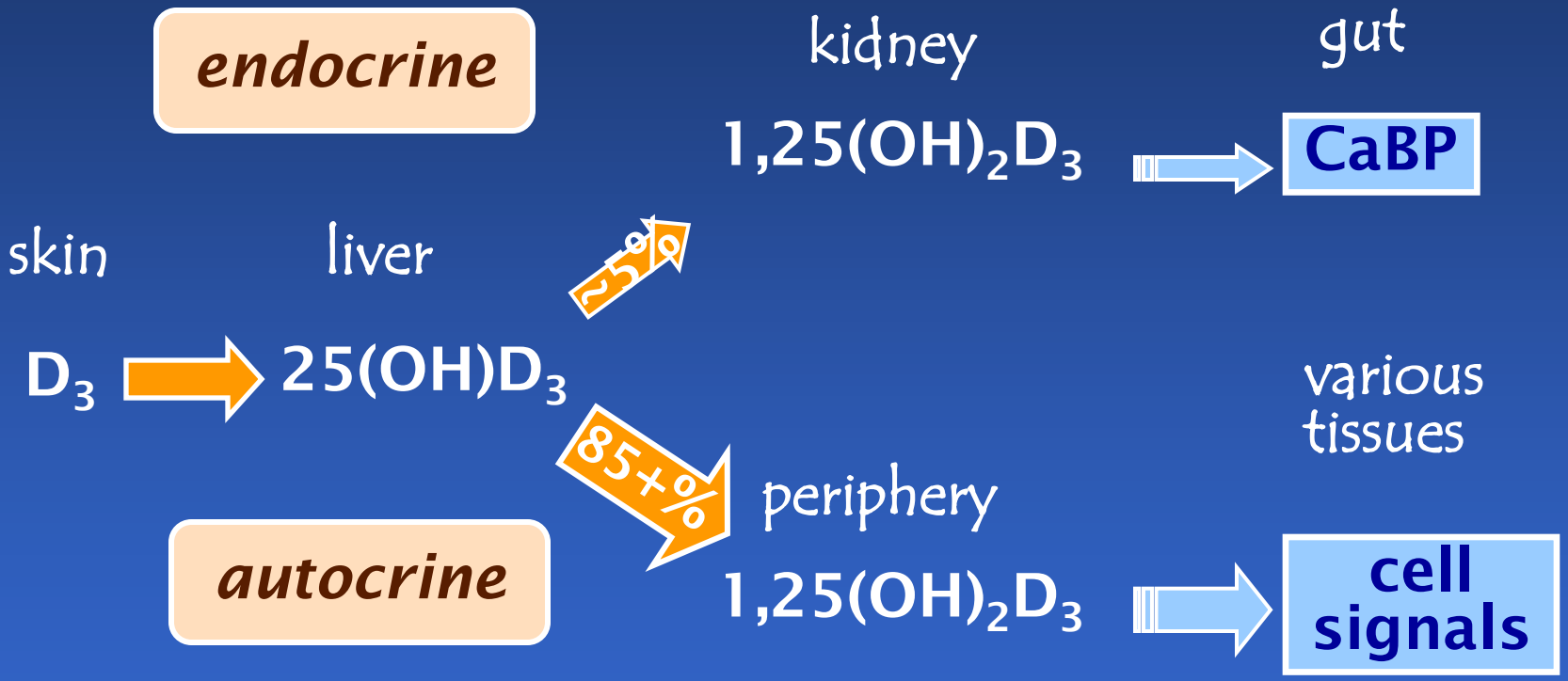
OLD VIT D – CANONICAL SCHEME

skin liver kidney gut

VIT D – EXPANDED SCHEME



VIT D – EXPANDED SCHEME



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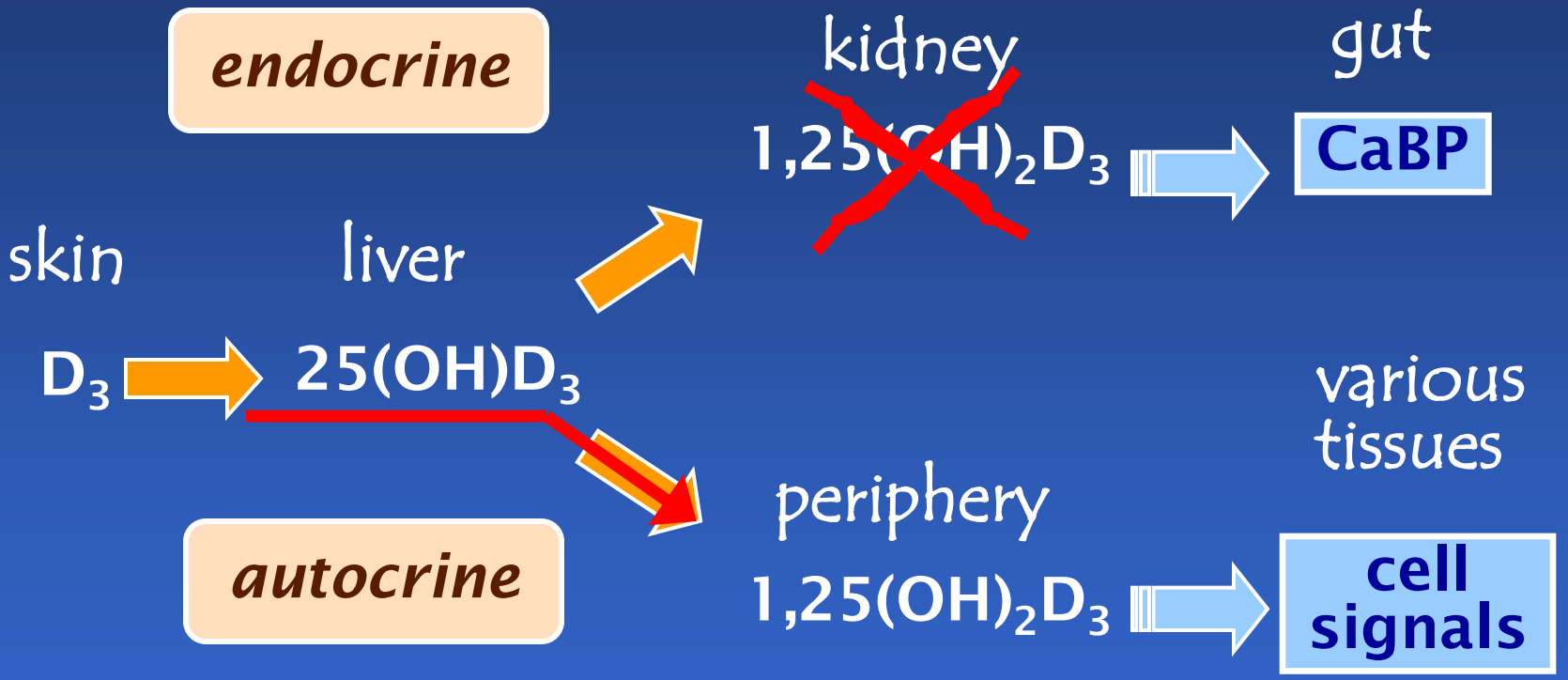

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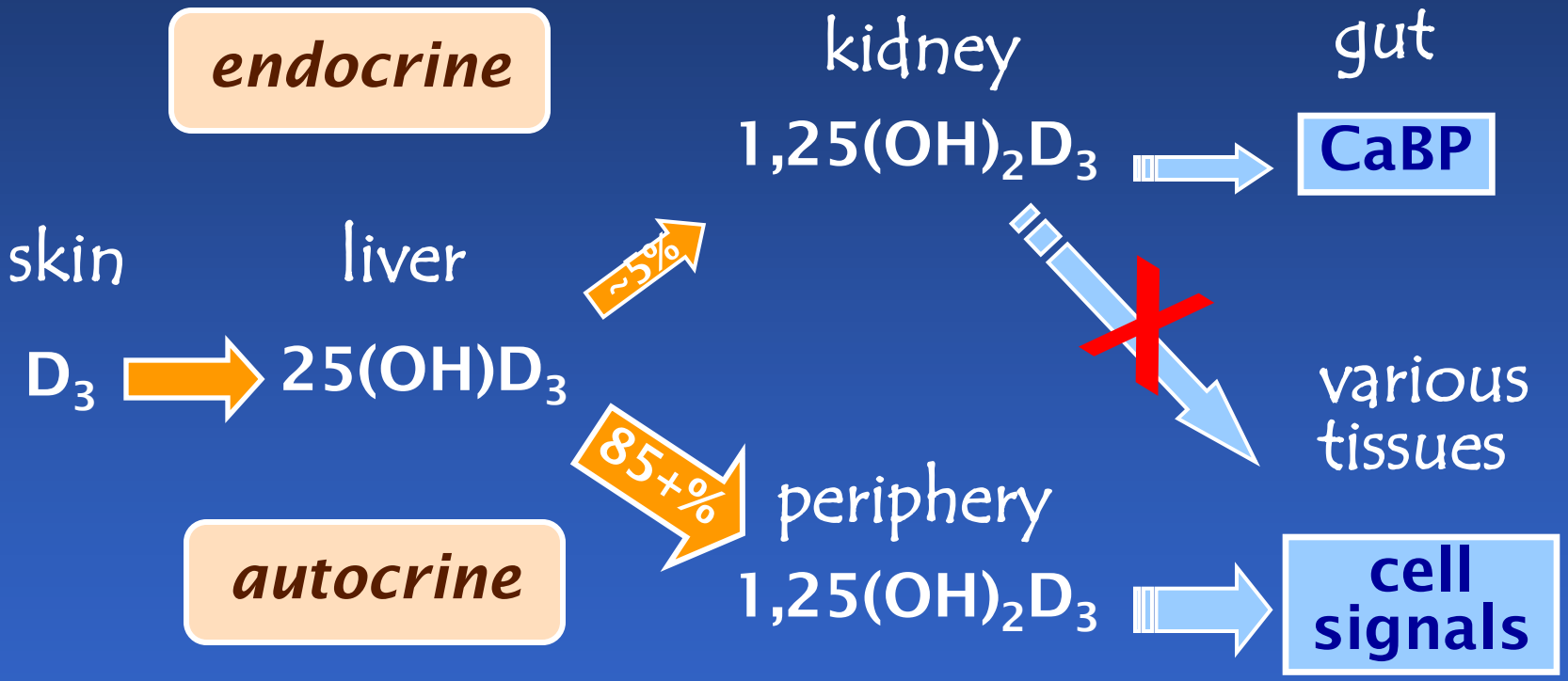
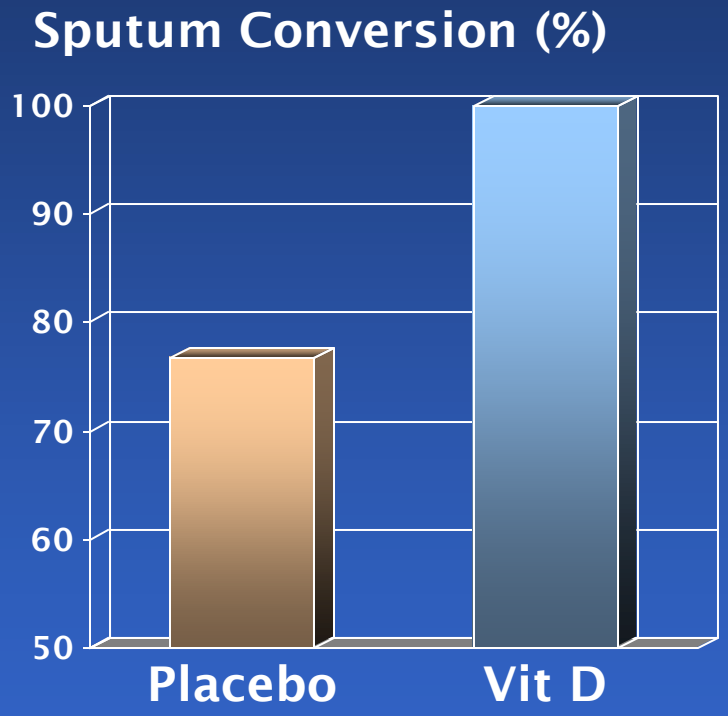


VITAMIN D & TUBERCULOSIS*

- 67 pts with pulmonary TB
- standard treatment for all
- In addition, randomized to either vit D 10,000 IU/d or placebo
- P = 0.002



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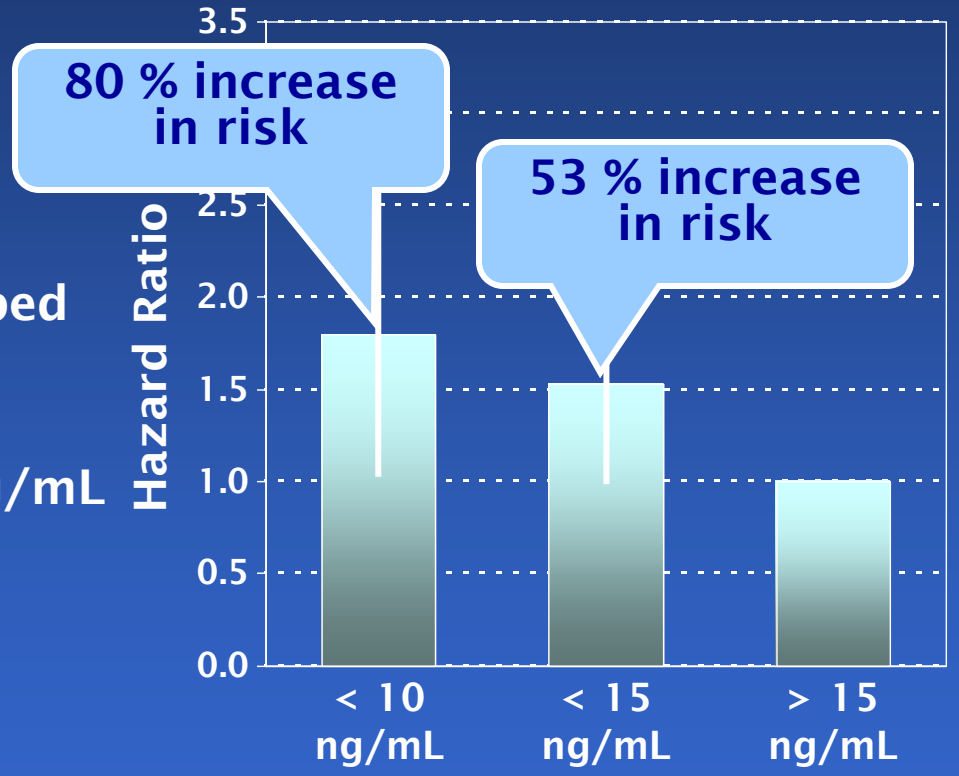
*Nursyam et al., Acta Med Indones 2006

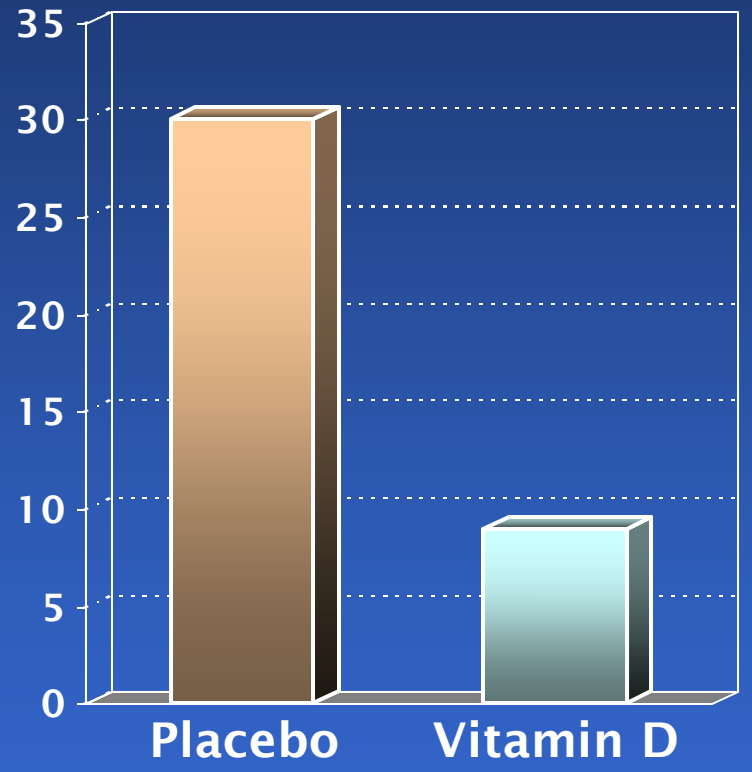
VIT D & CARDIOVASCULAR DISEASE

- 1739 Framingham Offspring members
- age: 59 yrs
- follow-up: 5.4 yrs
- 120 individuals developed a CV event
- HR calculated against 25(OH)D values > 15 ng/mL
- *Wang et al. Circulation 2008*



VITAMIN D & INFLUENZA*

- 208 African-American, postmenopausal women
- 3 yr DB-RCT
- placebo or vit D_3
  - 800 IU/d – 2 yrs
  - 2000 IU/d – 3rd yr
- basal 25(OH)D: 18.8 ± 7.5
- P < 0.002



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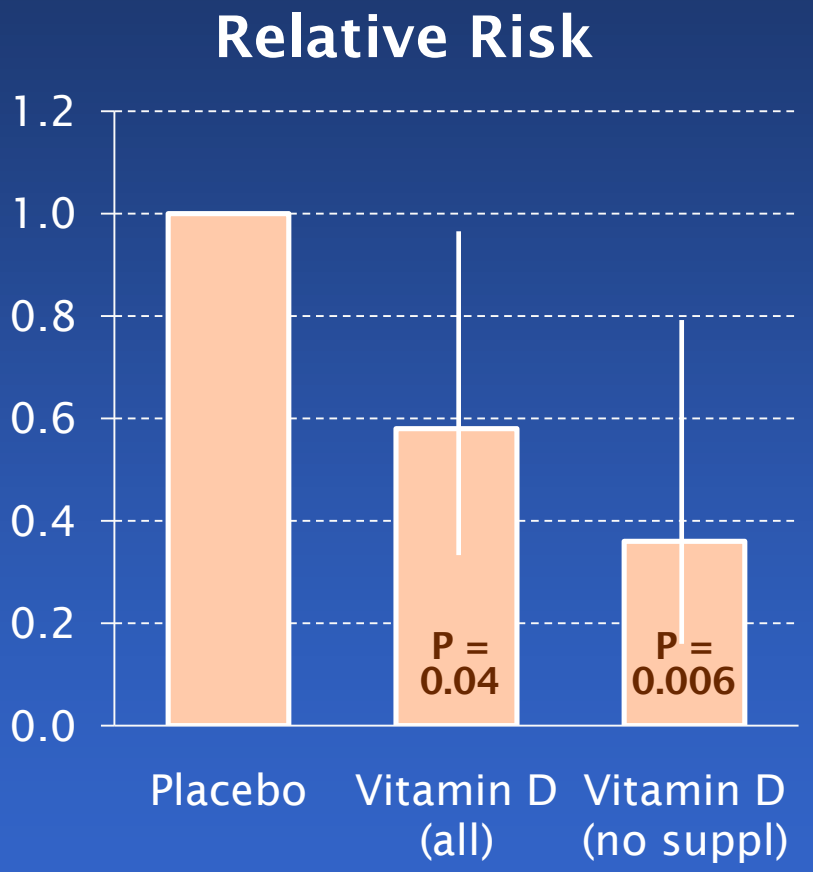
*Aloia & U-Ng (2007) Epidemiol & Infect

VITAMIN D & INFLUENZA*

- DB-RCT
- winter 2008-2009
- 334 Japanese school children, aged 6-15
- mean wt: 35.5 kg
- 1200 IU D_3/d in addition to self-supplementation



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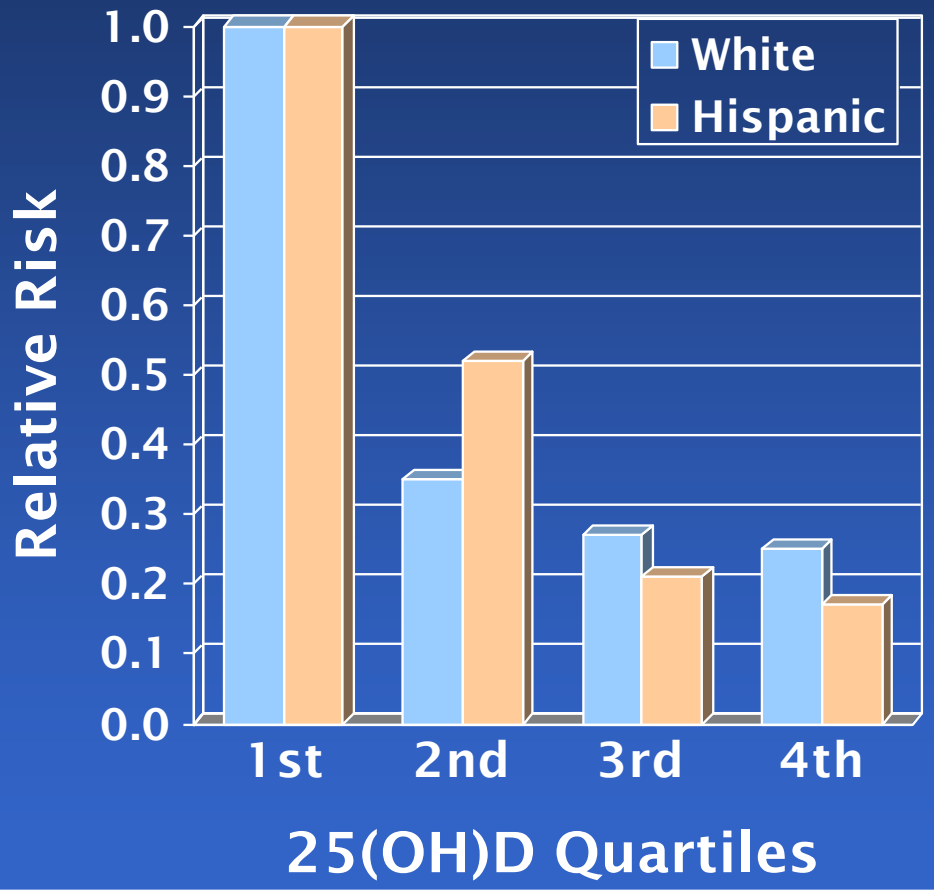
*Urashima et al., AJCN 2010

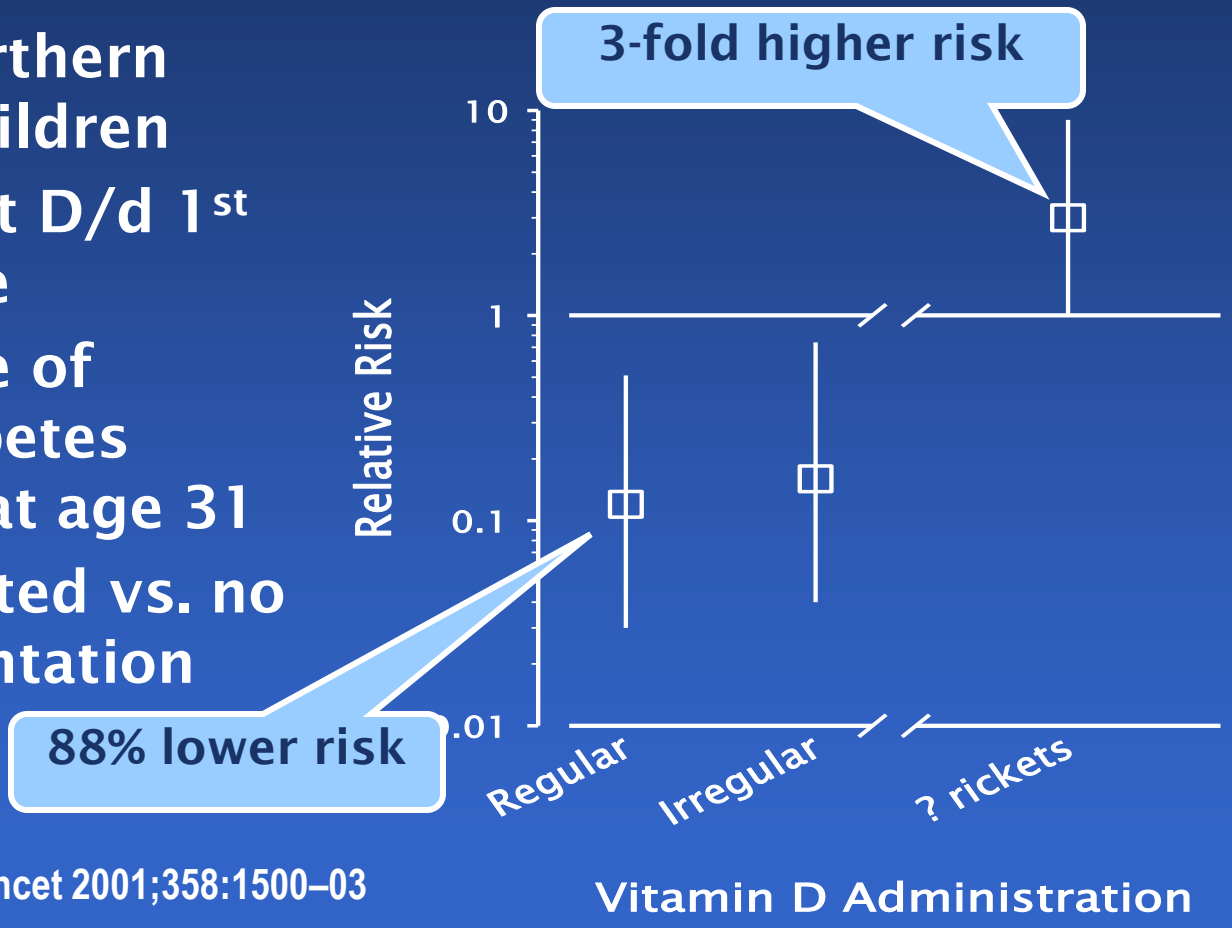
DIABETES & 25(OH)D

- Scragg et al., 2004 Diabetes Care 27:2813-18
- NHANES-III
- 6,228 adults
- plasma glucose independently predicted by BMI & serum 25OHD (fasting and 2 hr post load)



NEONATAL VIT D & DIABETES*

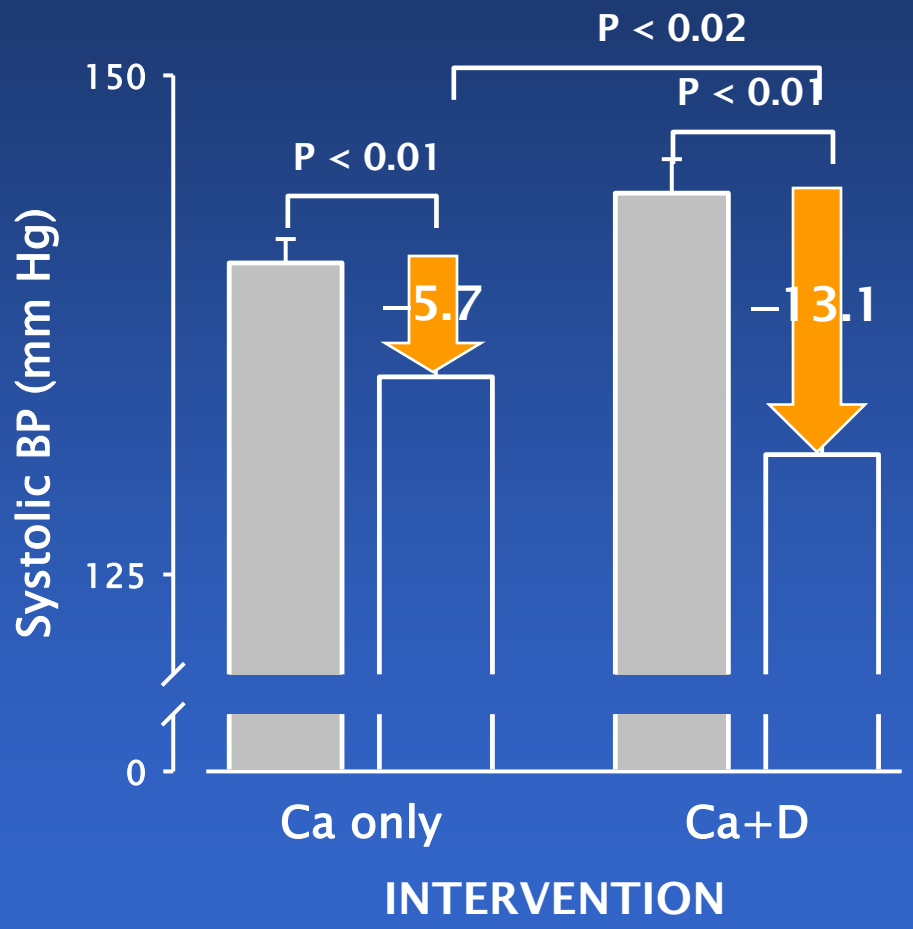
- 10,366 northern Finnish children
- 2000 IU Vit D/d 1st year of life
- prevalence of type I diabetes assessed at age 31
- RR calculated vs. no supplementation



*Hypponen et al., Lancet 2001;358:1500–03

VIT D & BLOOD PRESSURE*

- 148 women, aged 74 ± 1
- DB-RCT
- baseline 25(OH)D < 50 nmol/L
- treated for 8 wks with:
  Ca 1200 mg/d or
  Ca + 800 IU vit D/d



*Pfeifer et al., JCEM 2001; 86:1633–37

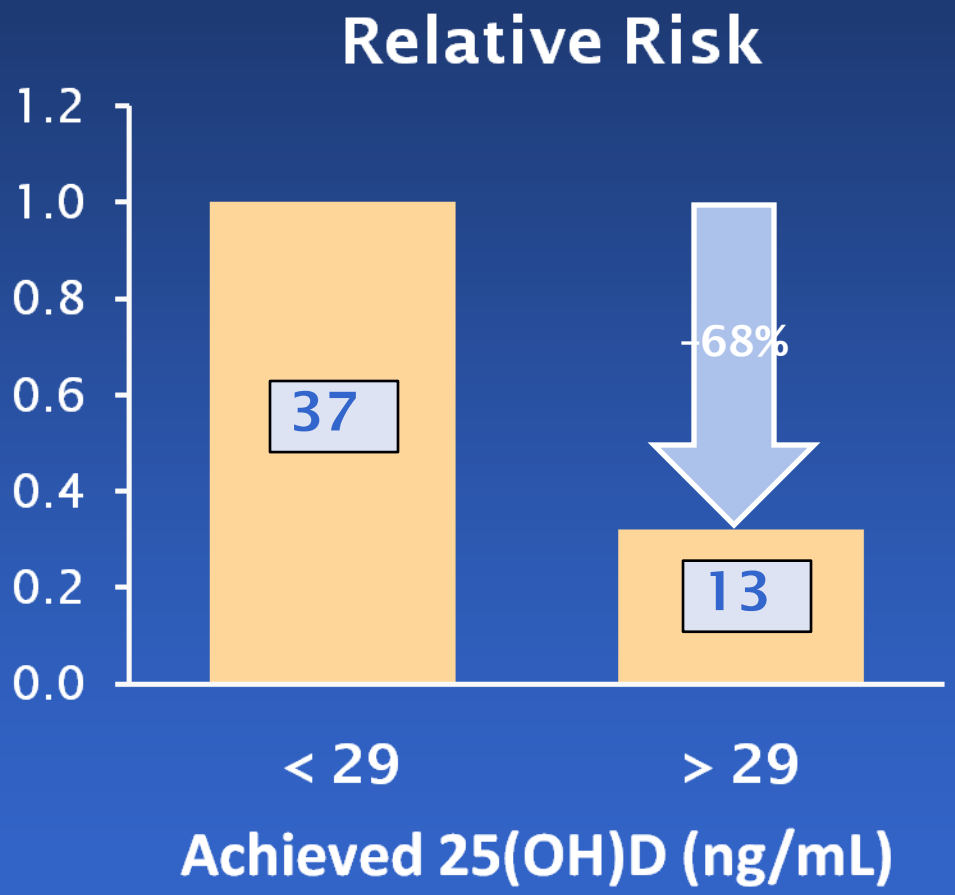
VITAMIN D & CANCER*

- 1179 healthy women
- aged 66.7 ± 7.3
- four year trial
- 1032 finished (87.5%)
- baseline 25(OH)D: 71.8 nmol/L ± 20.3
- three treatment groups:
  - control
  - Ca (1400–1500 mg/d)
  - Ca plus D_3 (1100 IU/d)
- achieved 25(OH)D: 96 nmol/L ± 21.4

*Lappe et al. AJCN 2007

CANCER RISK (ALL)

- N = 1,179
- ages 55–85
- 4 yr RCT
- Vit D ≅ 1100 IU/d
- *median* achieved serum 25(OH)D = 29 ng/mL
- Lappe et al. AJCN 2007

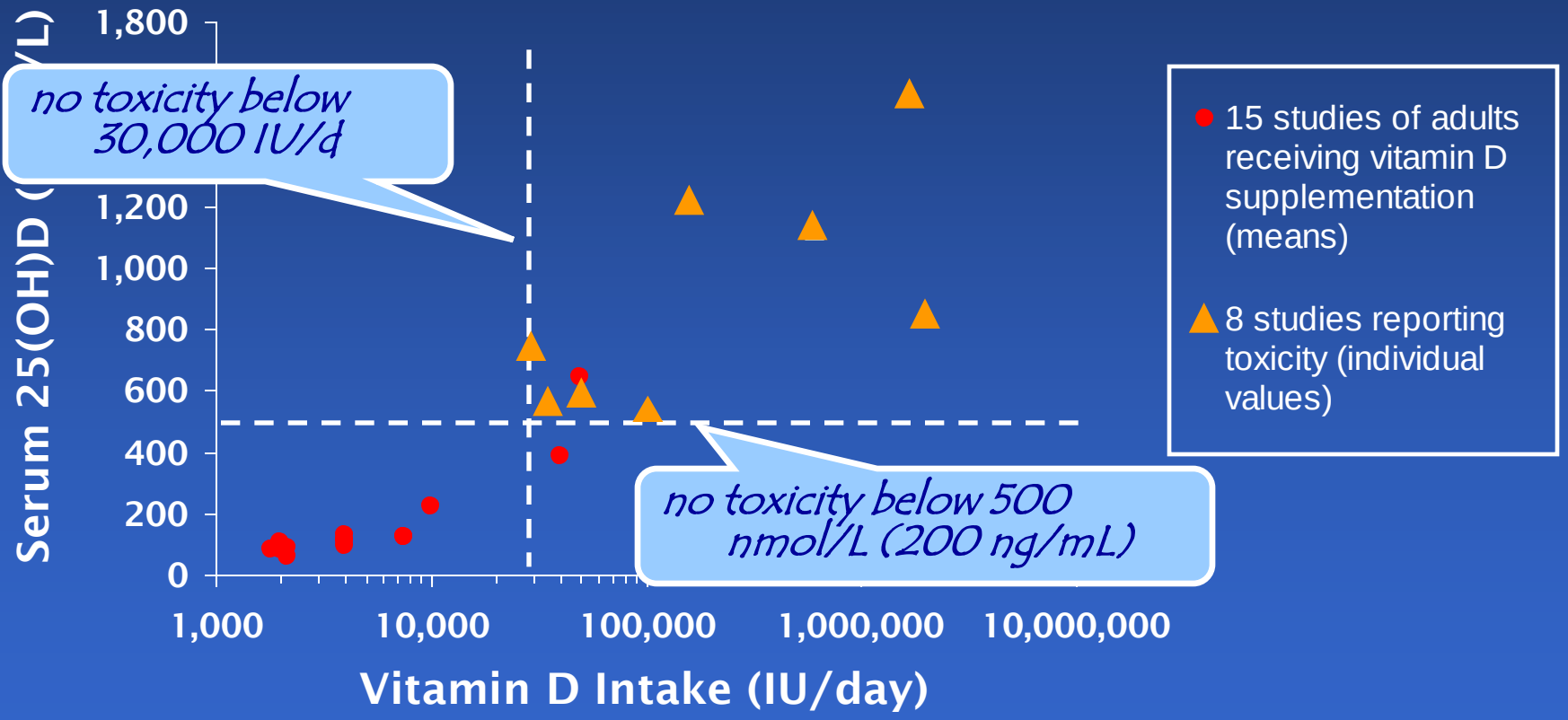


The preponderance of the evidence clearly indicates that vitamin D status above that which currently prevails confers important health benefits

HOW MUCH DO WE NEED?

- to maintain 40ng/mL, an adult needs about 5000 IU of D3/day
- if we work outdoors, have considerable exposed skin, and do not use sunscreen, we could make most of that for ourselves
- otherwise we'll need supplements – typically 1000–3000 IU/day
  - dosing can be daily, weekly, or monthly

VITAMIN D INTAKE & TOXICITY*



* Hathcock JN et al. *Am J Clin Nutr*. 2007;85:6–18.

SUMMARY

- for several body systems the preponderance of the evidence indicates that ≥32 ng/mL is needed for the full benefits of vitamin D
- observational studies support this conclusion and strengthen the level 1 evidence by insuring the generalizability of the RCTs
- for some endpoints (e.g., cancer) the data suggest that even 32 ng/mL is not high enough (40 – 60 is preferable)

SUMMARY

- levels of 40 ng/mL & above are physiological
- given the manifest safety of such levels, we should strive to achieve at least 40 ng/mL in all our patients & clients
- D_3 input from all sources should be about 75 IU/kg/d – all ages and body sizes

Thank you . . .