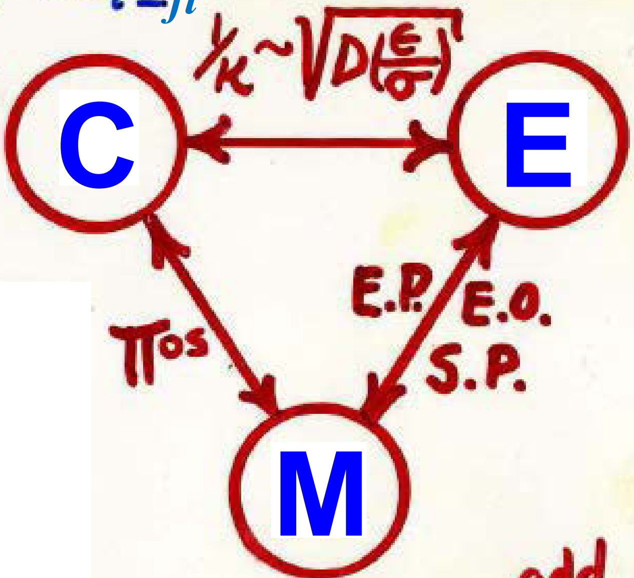
FFF: Complete Description of Coupled Transport and Biomolecular Interactions

$$\underline{N}_i = -D_i \nabla c_i + \frac{z_i}{|z_i|} u_i c_i \underline{E} + c_i \underline{v}_{fl}$$

$$\frac{\partial c_i}{\partial t} = -\nabla \cdot \underline{N}_i + R_{vi}$$

Diffusion-Reaction



$$\nabla \cdot \epsilon \underline{E} = \rho_e = \sum_i z_i F c_i$$

$$(\underline{E} = -\nabla \Phi)$$

$$\nabla \cdot \underline{J} = -\frac{\partial \rho_e}{\partial t}$$

$$\underline{J} = \sum_i z_i F \underline{N}_i$$

"E.Q.S."

Navier Stokes

$$\rho_0 \frac{D\underline{v}}{Dt} = -\nabla p + \mu \nabla^2 \underline{v} + \rho_e \underline{E} + \ldots$$

add $(+\underline{P} \cdot \nabla \underline{E}) + \ldots +$ other

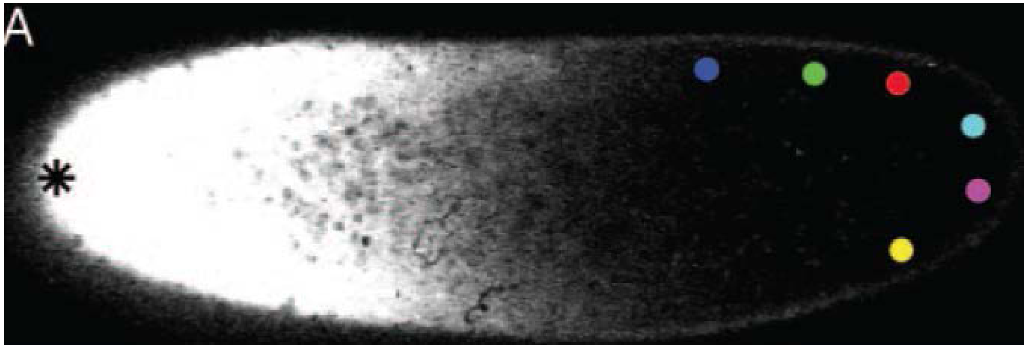
$\nabla \cdot \underline{v} = 0$ (incomp. fluid)

(where $\frac{D\underline{v}}{Dt} = \frac{\partial \underline{v}}{\partial t} + (\underline{v} \cdot \nabla)\underline{v}$)

Diffusion and scaling during early embryonic pattern formation

PNAS | December 20, 2005

Thomas Gregor*†‡§¶, William Bialek*†, Rob R. de Ruyter van Steveninck‖, David W. Tank*†‡, and Eric F. Wieschaus‡§¶



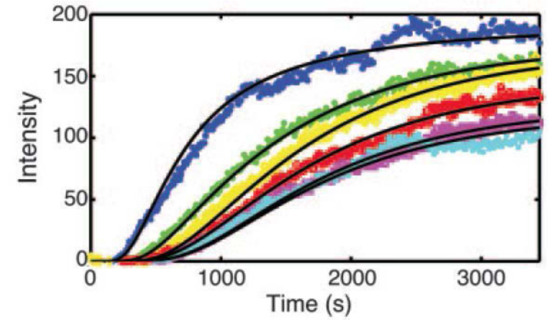
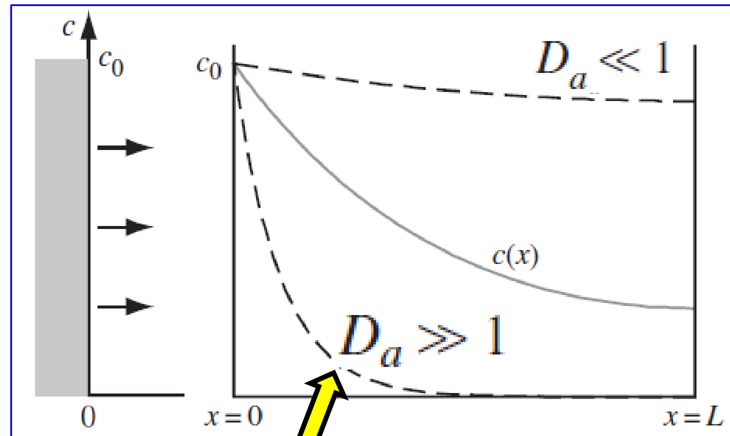


Fig. 1. Diffusion in Drosophila embryo

$$\frac{\partial c}{\partial t} = D\nabla^2 c \underbrace{-kc}_{+R}$$

$$\frac{d^2 c}{dx^2} = \frac{k}{D} c$$

$$\frac{d^2 \hat{c}}{d\hat{x}^2} - \frac{L^2 k}{D}\hat{c} = 0$$

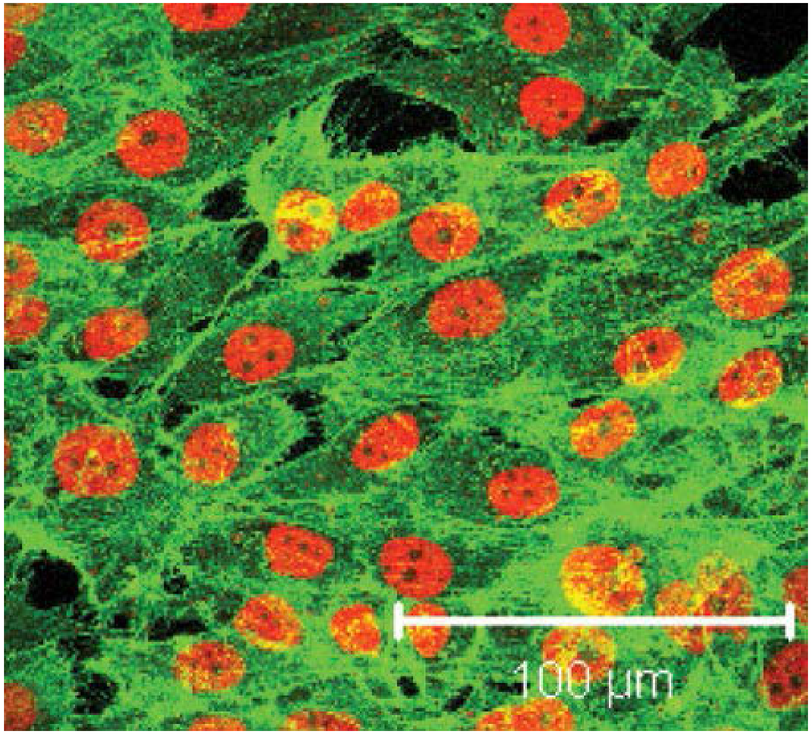


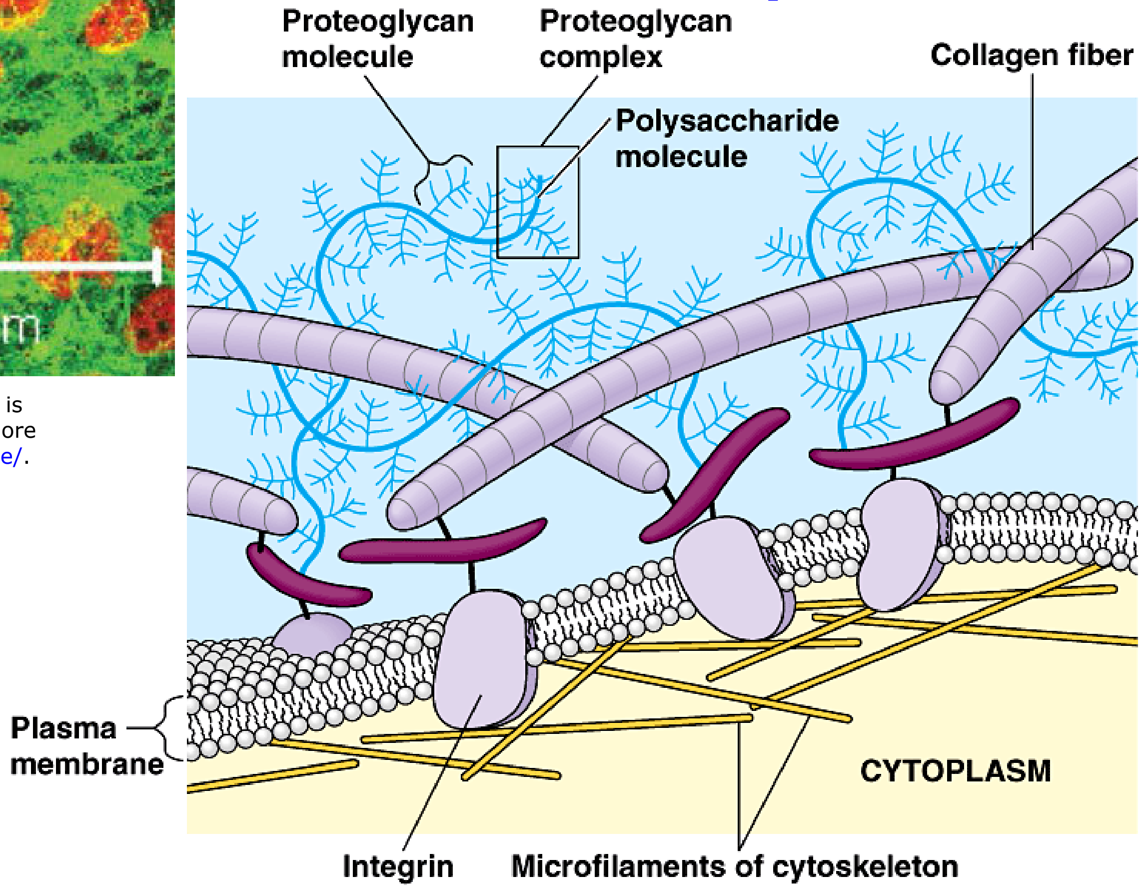
Slow diffusion; fast reaction

$$D_a = \frac{\text{characteristic diffusion time}}{\text{characteristic reaction time}} = \frac{L^2/D}{k^{-1}}$$

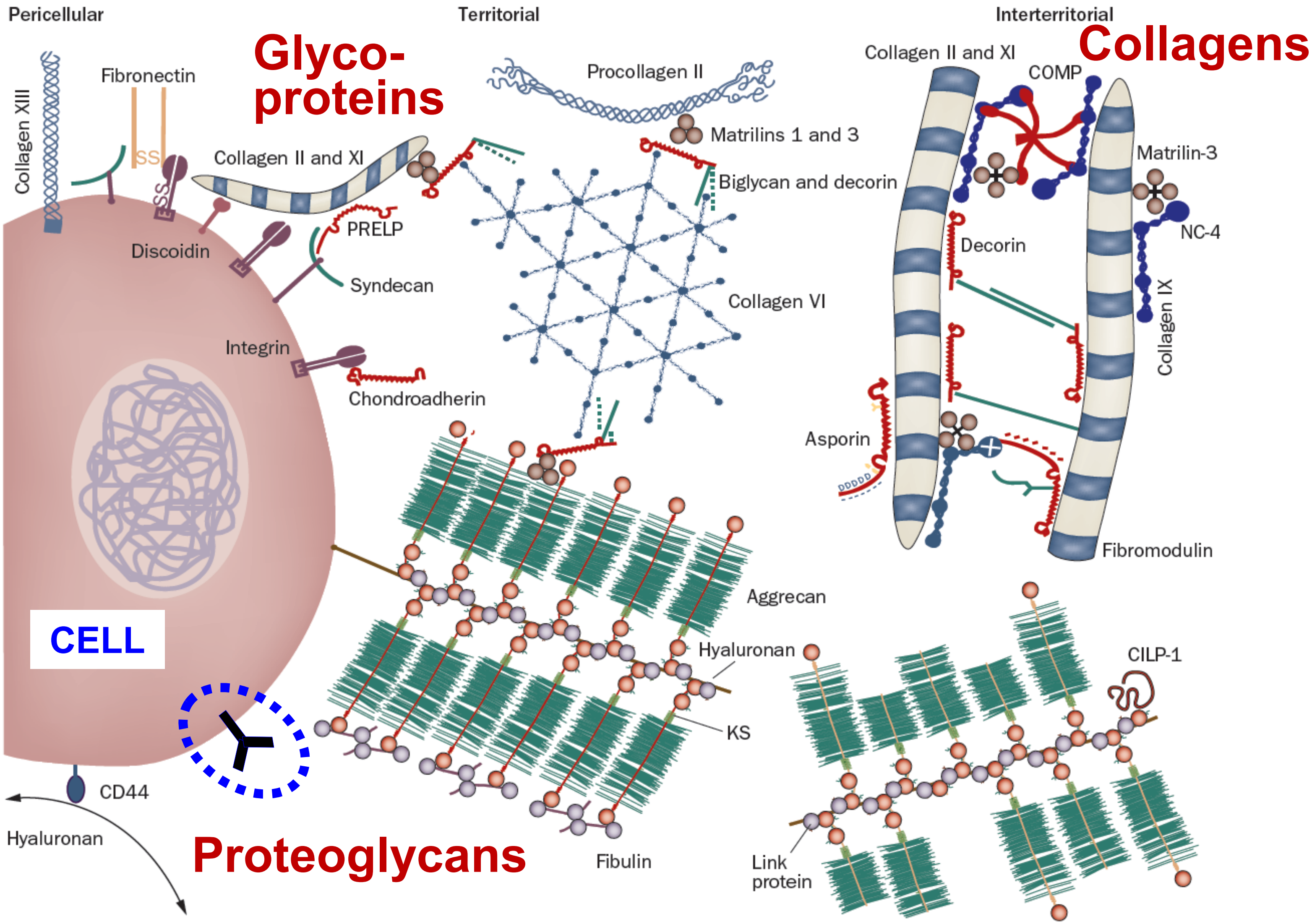
Source: Gregor, Thomas et al. "Diffusion and scaling during early embryonic pattern formation." Proceedings of the National Academy of Sciences of the United States of America 102, no. 51 (2005): 18403-18407.

Growth factors (e.g., IGF-1) and cytokines (e.g., TNFα) can bind to Extracellular Matrix molecules as well as cell receptors





Cells live in a rich Extracellular Matrix



(Dick Heinegård & Tore Saxne, Nature Revs. Rheumatology 2010)

Overview of the Matrisome—An Inventory of Extracellular Matrix Constituents and Functions

Richard O. Hynes and Alexandra Naba

CSH PERSPECTIVES Cold Spring Harbor Perspectives in Biology 2012

Howard Hughes Medical Institute, Koch Institute for Integrative Cancer Research, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139

- Completion of the genome for many organisms allows a complete definition of extracellular matrix (**ECM**) proteins.
- **In mammals this "core matrisome" comprises ~300 proteins**.
- Also: there are many **ECM-binding growth factors**, ECM modifying enzymes, ECM modifying cytokines….

Insulin-like Growth Factor-1 (IGF-1)

- Peptide Growth Factor:
  - ♦ Stimulates cellular biosynthesis;
  - ♦ Inhibits catabolic degradation of ECM
- Protein: **7.6 kDa (70 amino acids)**
- "Folds" like Insulin in Aq. Solution
- **pI ~ 8.4** ("basic" + charged @ pH 7)
- **Found in: Nerve, Muscle, Connective, & Epithelial Tissues**
  - ♦ Serum (50-200 ng/ml)
  - ♦ Joint Fluid (20-50 ng/ml)
  - ♦ Tissue (1-10 ng/ml)

.....including BRAIN

Biochemistry, Vol. 40, No. 37, 2001 11025

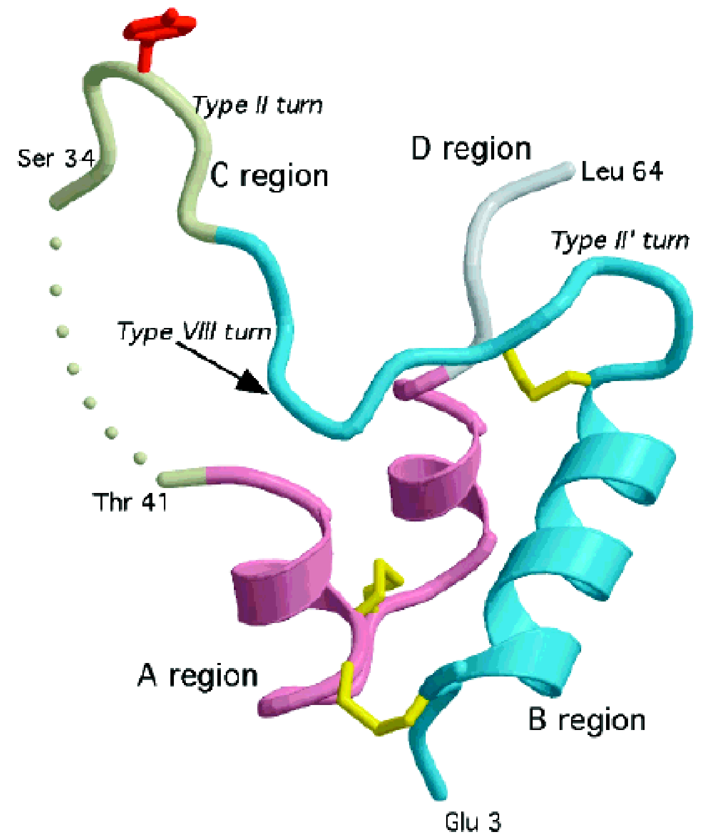
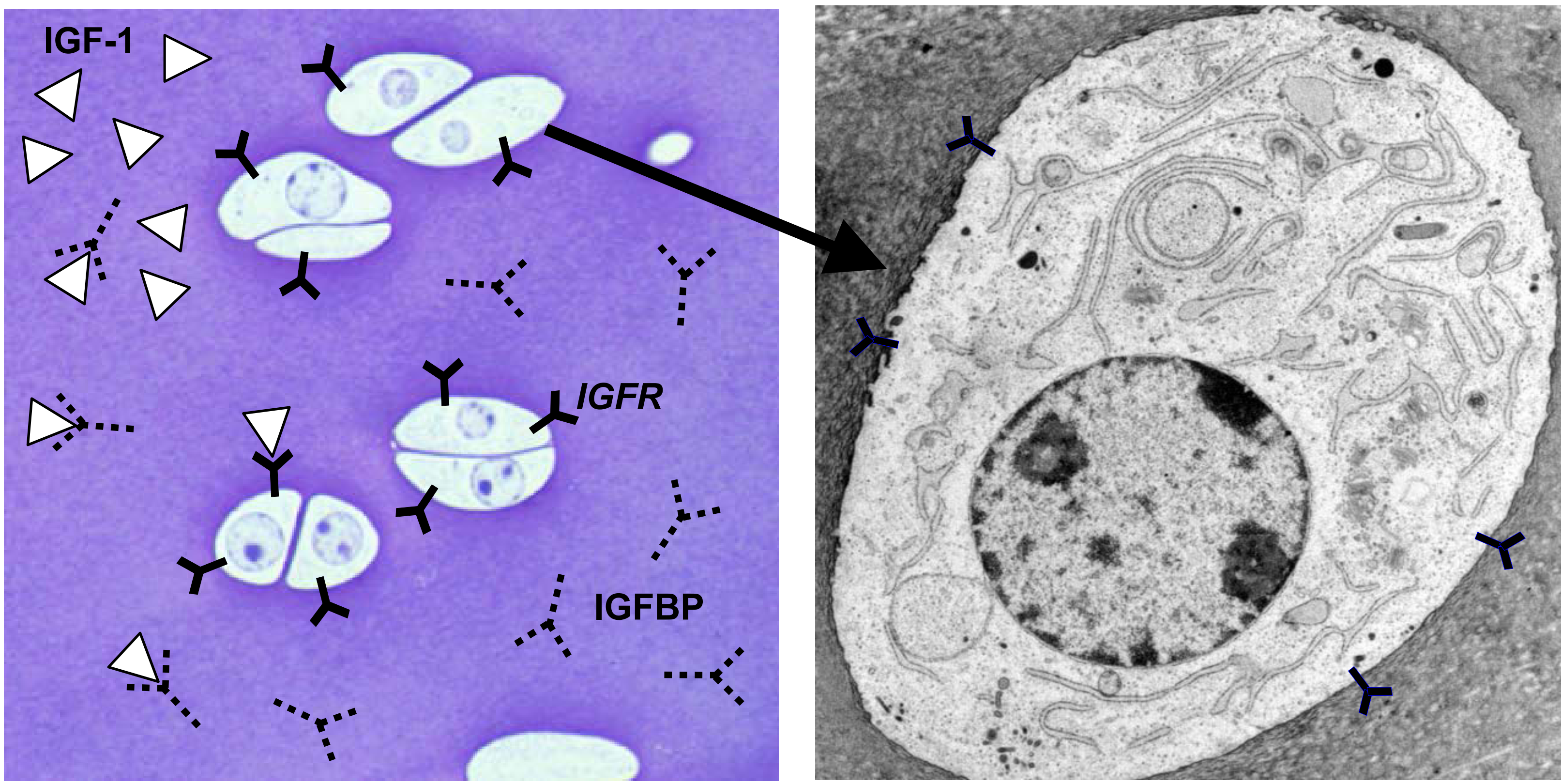


FIGURE 1: Ribbon structure of IGF-1. The B-region (residues 3–28)

Source: Vajdos, Felix F. et al. "Crystal structure of human insulin-like growth factor-1: detergent binding inhibits binding protein interactions." Biochemistry 40, no. 37 (2001): 11022-11029.

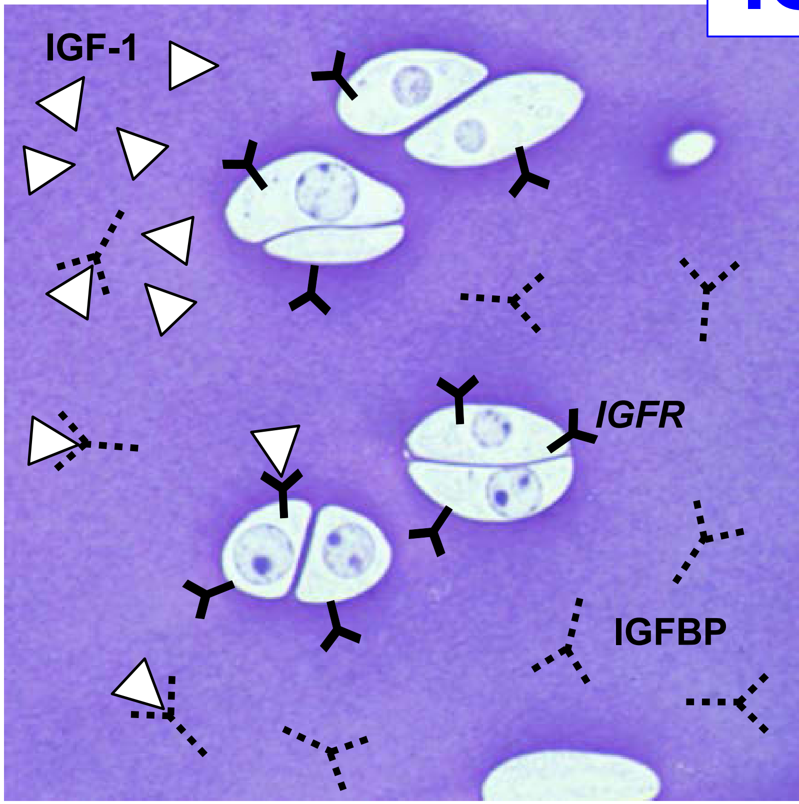
IGF-1 Transport: stimulate anabolic response

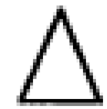
(1) Through dense **<u>tissue Extracellular Matrix</u>** (ECM) of **<u>collagens, proteoglycans, glycoproteins</u>**… **to cell**



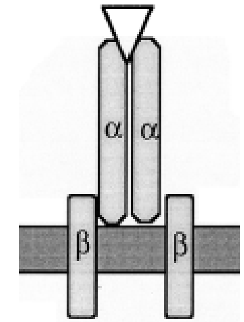
(2) <u>Binding Sites</u>:
- **Cell surface receptors (~10,000 / cell!)**
- **IGF binding proteins**

IGF System

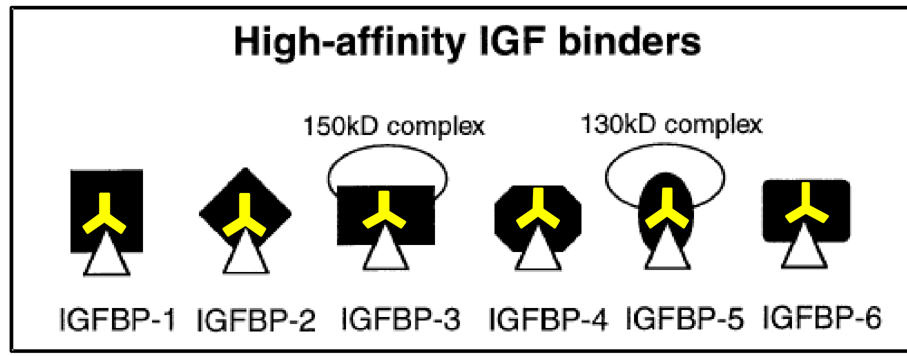


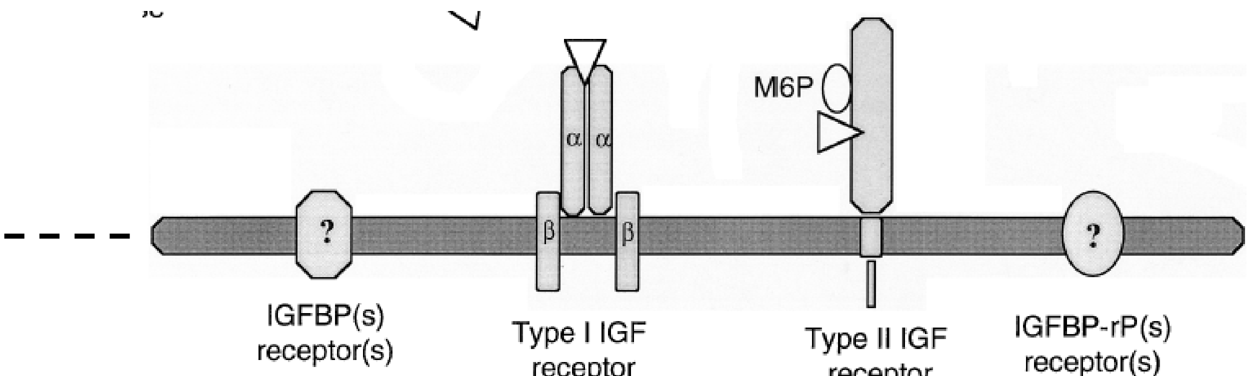


IGF-I/II



Type I IGF receptor





Outside the Cell

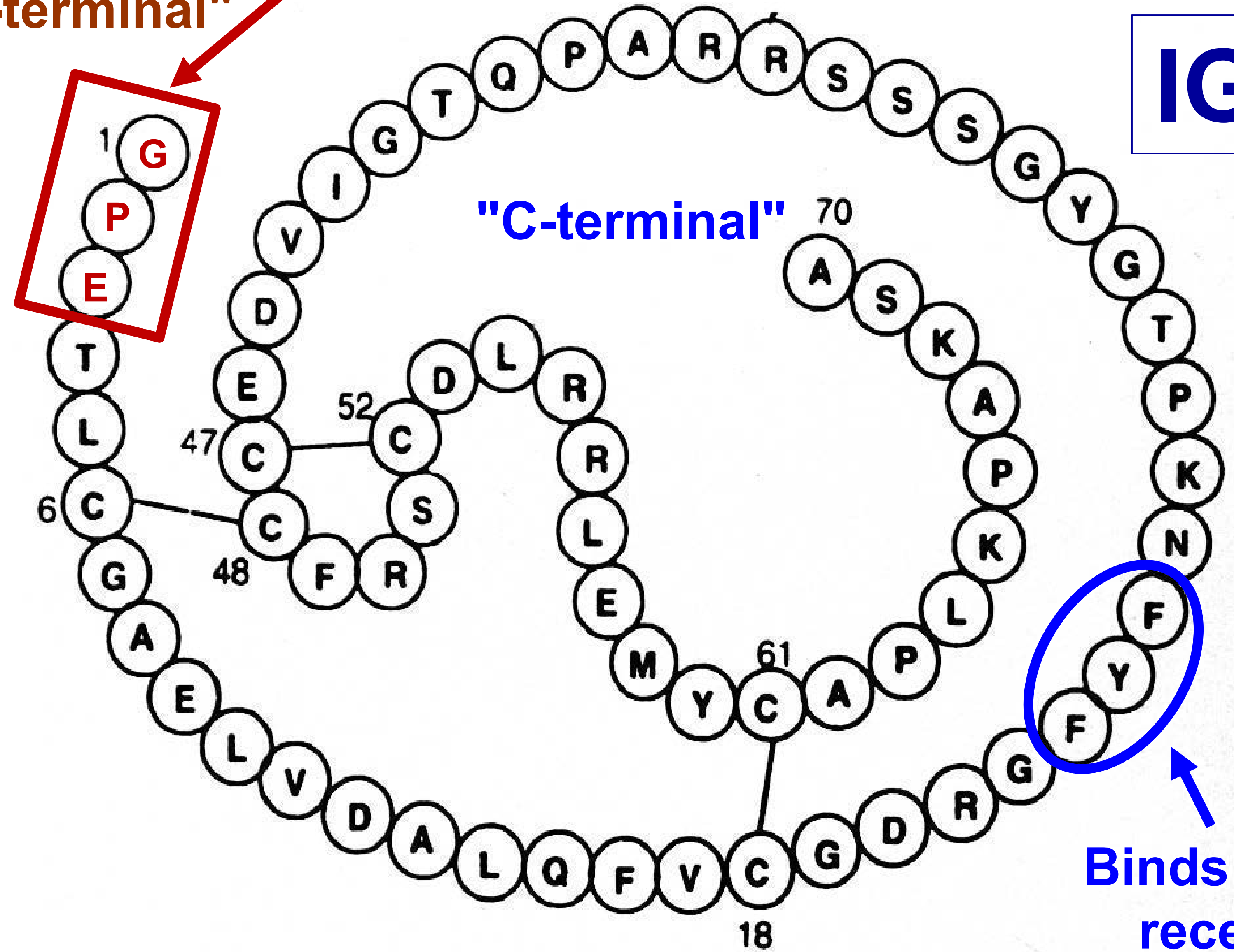
Inside the Cell

IGF-1

(**G** = glycine; **P**=proline; **E**=glutamic acid)

Binds to IGFBPs

"N-terminal"



Binds to Cell receptor

(Phe [23] Tyr [24] Phe [25])

(**F** = Phe = phenylalanine; **Y** = Tyr = tyrosine)

SIMONS CENTER
FOR THE SOCIAL BRAIN

SFARI SIMONS FOUNDATION AUTISM RESEARCH INITIATIVE

Partial reversal of Rett Syndrome-like symptoms in MeCP2 mutant mice

PNAS 2009

Daniela Tropea[a,1], Emanuela Giacometti[b,1], Nathan R. Wilson[a,1], Caroline Beard[b], Cortina McCurry[a], Dong Dong Fu[b], Ruth Flannery[b], Rudolf Jaenisch[b,c,2], and Mriganka Sur[a,2]

[a]Picower Institute for Learning and Memory and Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge, MA 02139; [b]Whitehead Institute for Biomedical Research, Cambridge, MA 02142; and [c]Department of Biology, Massachusetts Institute of Technology, Cambridge, MA 02139

- **Rett patients express aberrantly high levels of IGFBP3, which inhibits IGF-1 signaling. Depressed IGF-1 signaling has indeed been implicated in autism spectrum disorder**

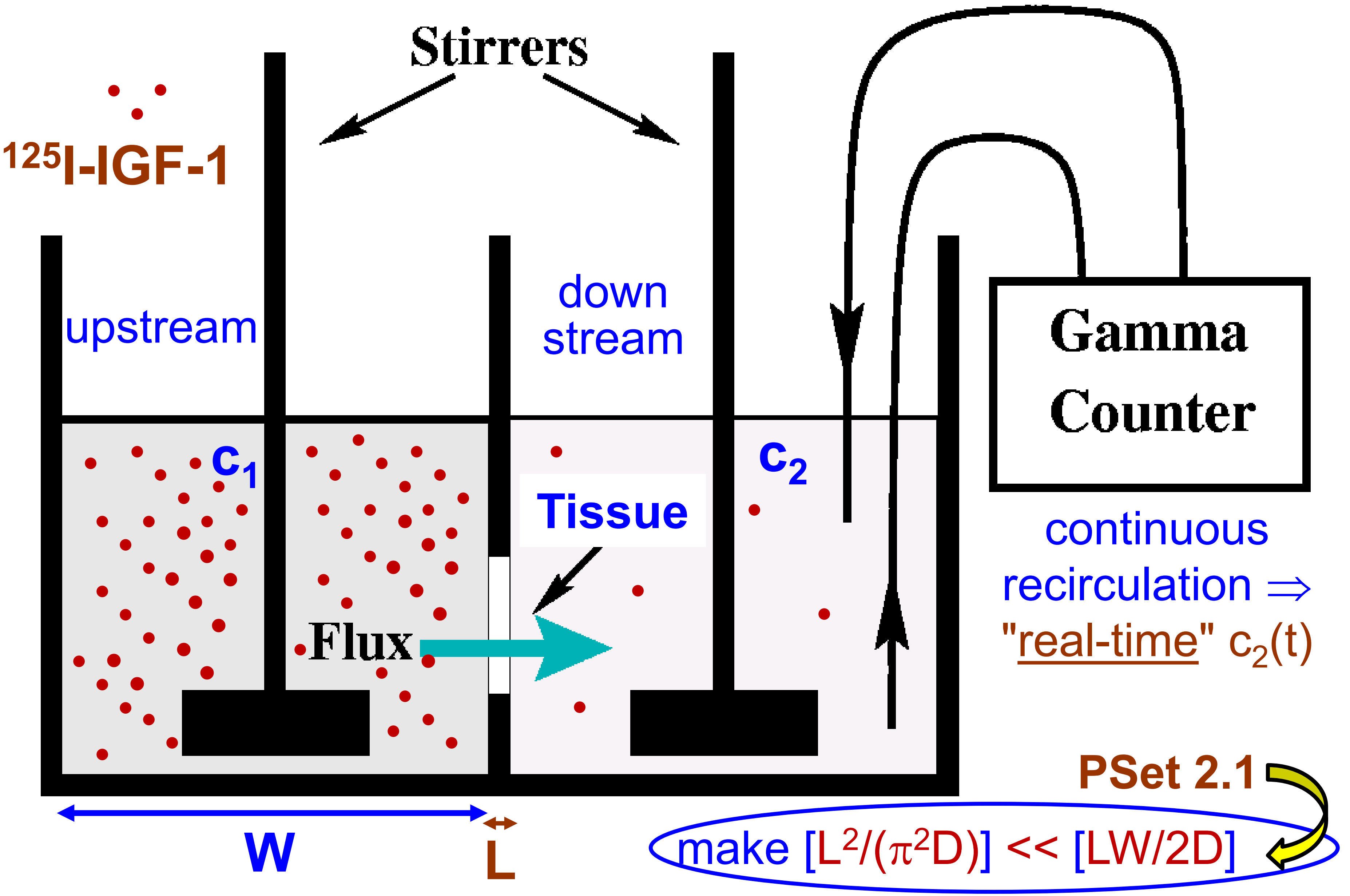
Phase 1 Trial: a small clinical trial at Mount Sinai School of Medicine in New York tested whether IGF-1 can treat some of the core symptoms of autism in children with Rett Syndrome.

…….Phase 1, 2013, completed: safety, **pharmacokinetics,** and preliminary assessment, …. "rh-IGF-1 is safe and well tolerated"……

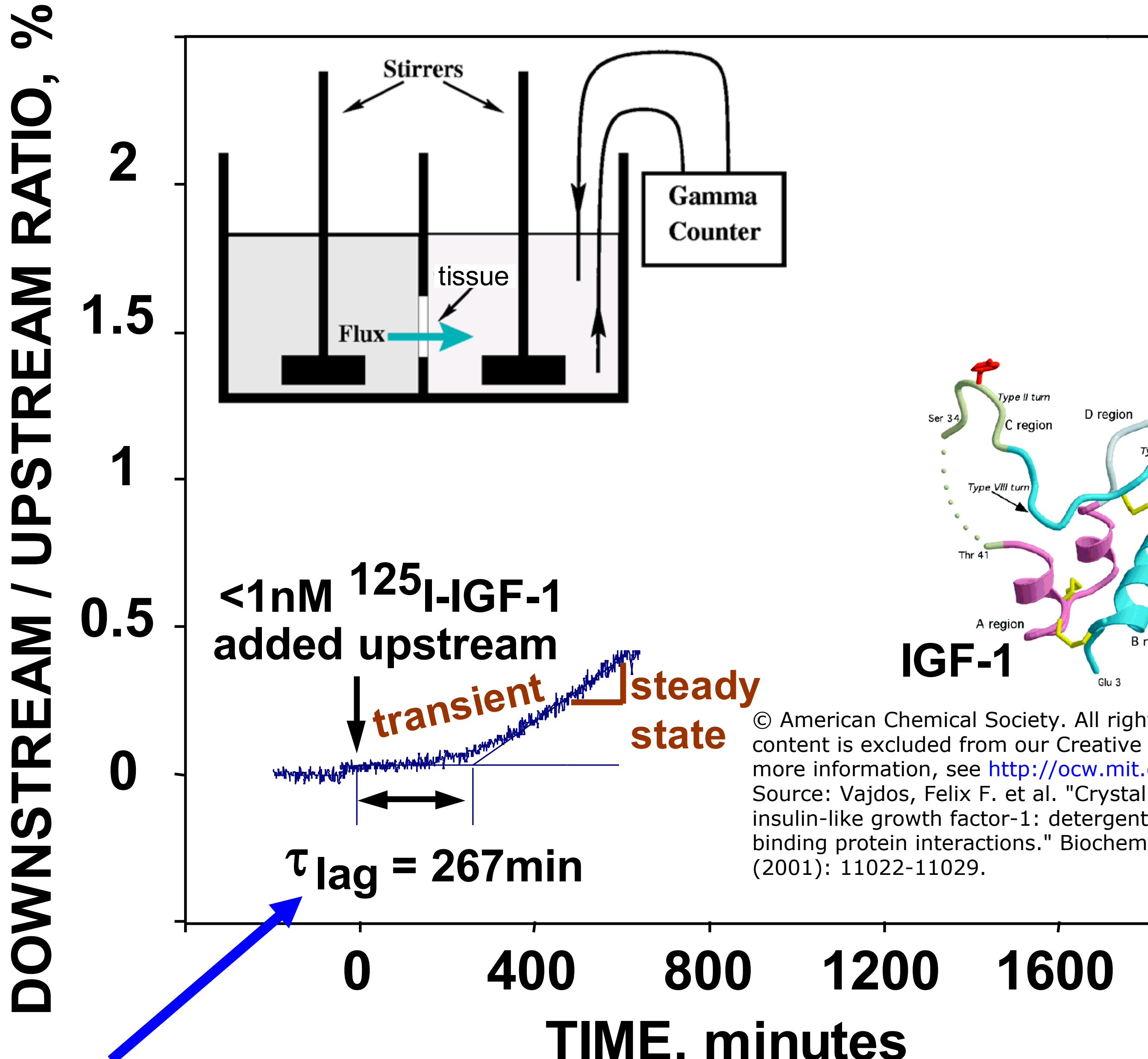
Phase 2 trial in progress at Boston Children's Hospital: includes 30 children with Rett syndrome between the ages of 2 to 10 years old who are in "stable" stage of the disease. Outcome measures include: breathing and behavior

Phase 2 trial is still ongoing; if successful, it will be followed by a larger replication Phase 3 study….as required for FDA approval…

Experimental Setup: Transport



IGFBP-3 Binding Slows entry of IGF-1 into Tissue!

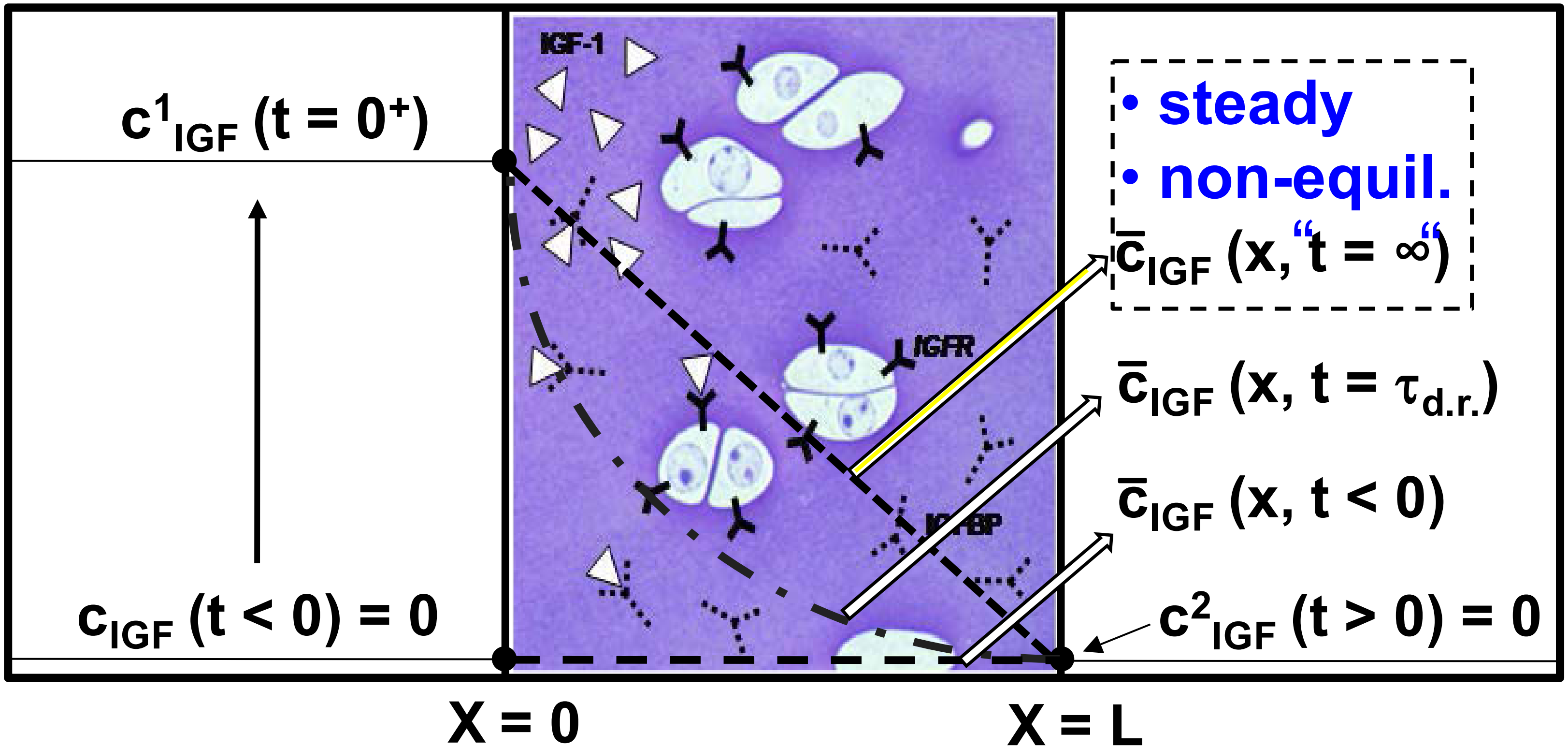


Source: Vajdos, Felix F. et al. "Crystal structure of human insulin-like growth factor-1: detergent binding inhibits binding protein interactions." Biochemistry 40, no. 37 (2001): 11022-11029.

$$\tau_{lag} = \frac{L^2}{6D_{eff}}$$

slow reaction, or slow diffusion compared to reaction???

Prob Set 1, Prob 4 (But neglected binding of IGF-1 to anything)



"Transient "

- **non-steady**
- **non-equil.**

$$\bar{c}_F(x,t) = c_1\left(1 - \frac{x}{L}\right) - \frac{2Kc_1}{\pi}\sum_{n=1}^{\infty}\left[\frac{1}{n}\right]\sin\left(\frac{n\pi x}{L}\right)e^{-t/\tau_n} \qquad (1.72)$$

$$\tau_n = \frac{L^2}{n^2\pi^2 D_{\text{eff}}} \qquad \boxed{\tau_1 = \frac{L^2}{\pi^2 D_{\text{eff}}}} \qquad (1.73)$$

Brain and Tissue Matrices

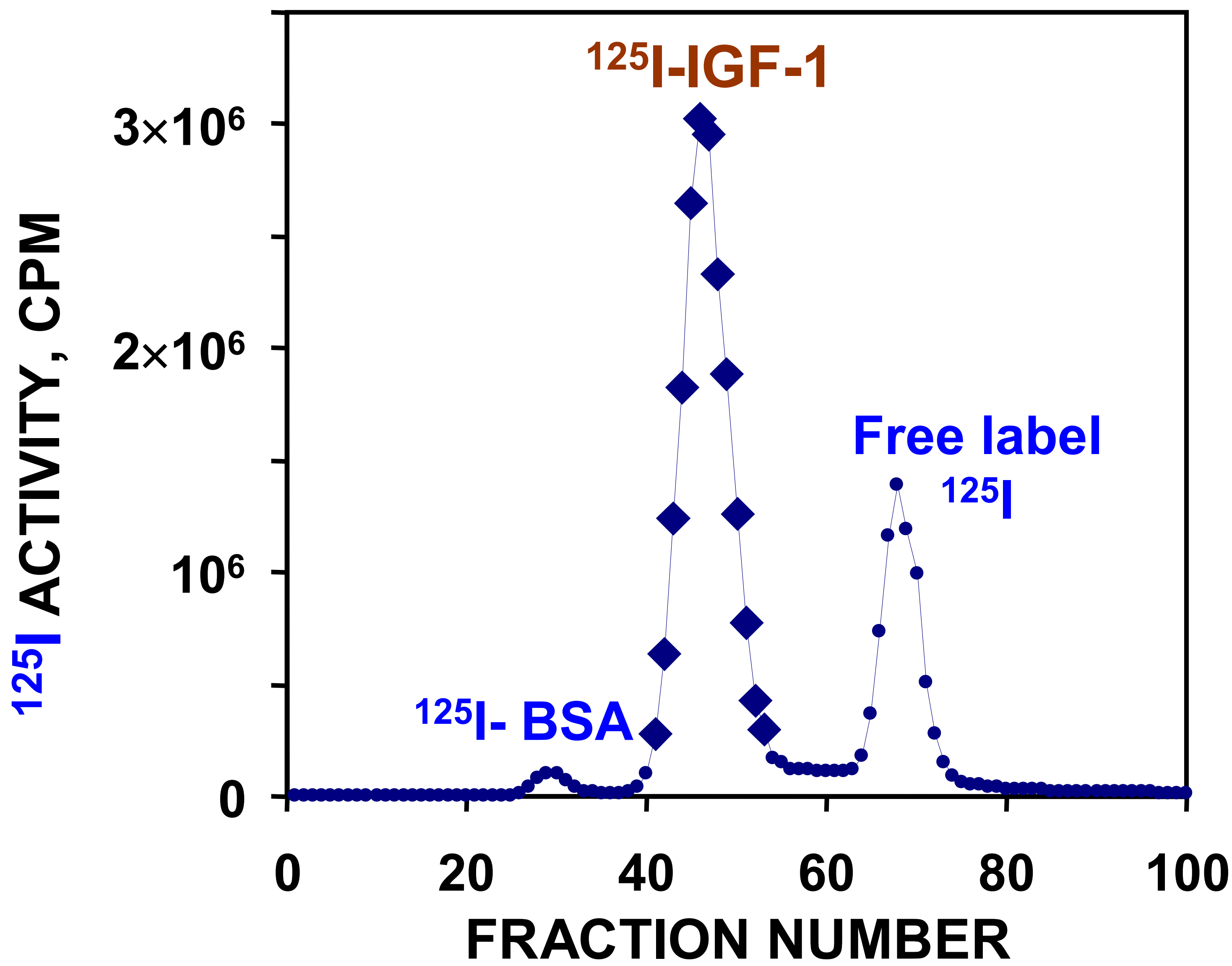
for neurophysiology, anatomy, biochemical pharmacology

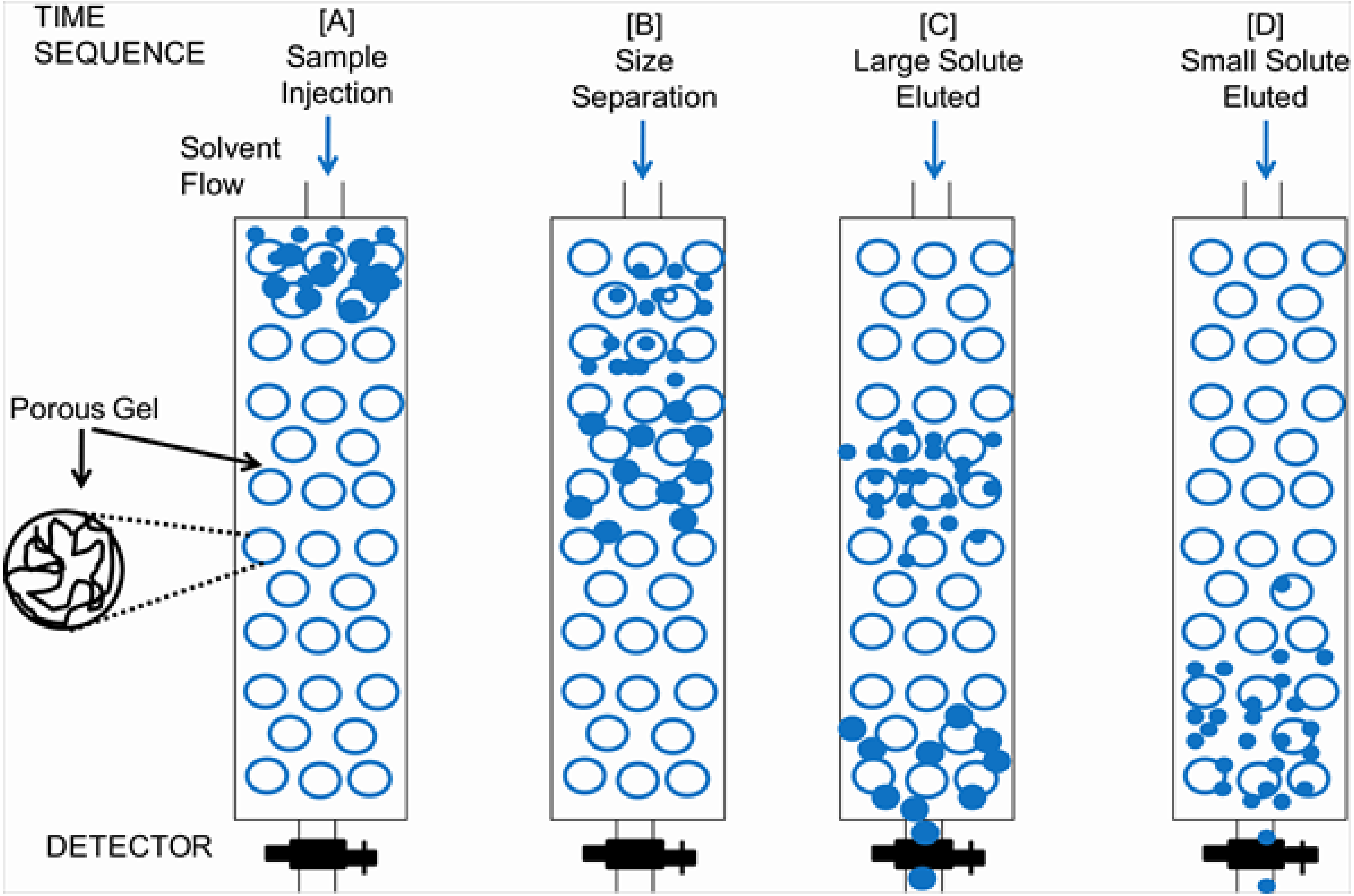
[Brain and Tissue Matrices] [Stainless Steel Matrices] [Acrylic Brain Matrices]

Slice thickness "L" ~ 200 – 500 μm

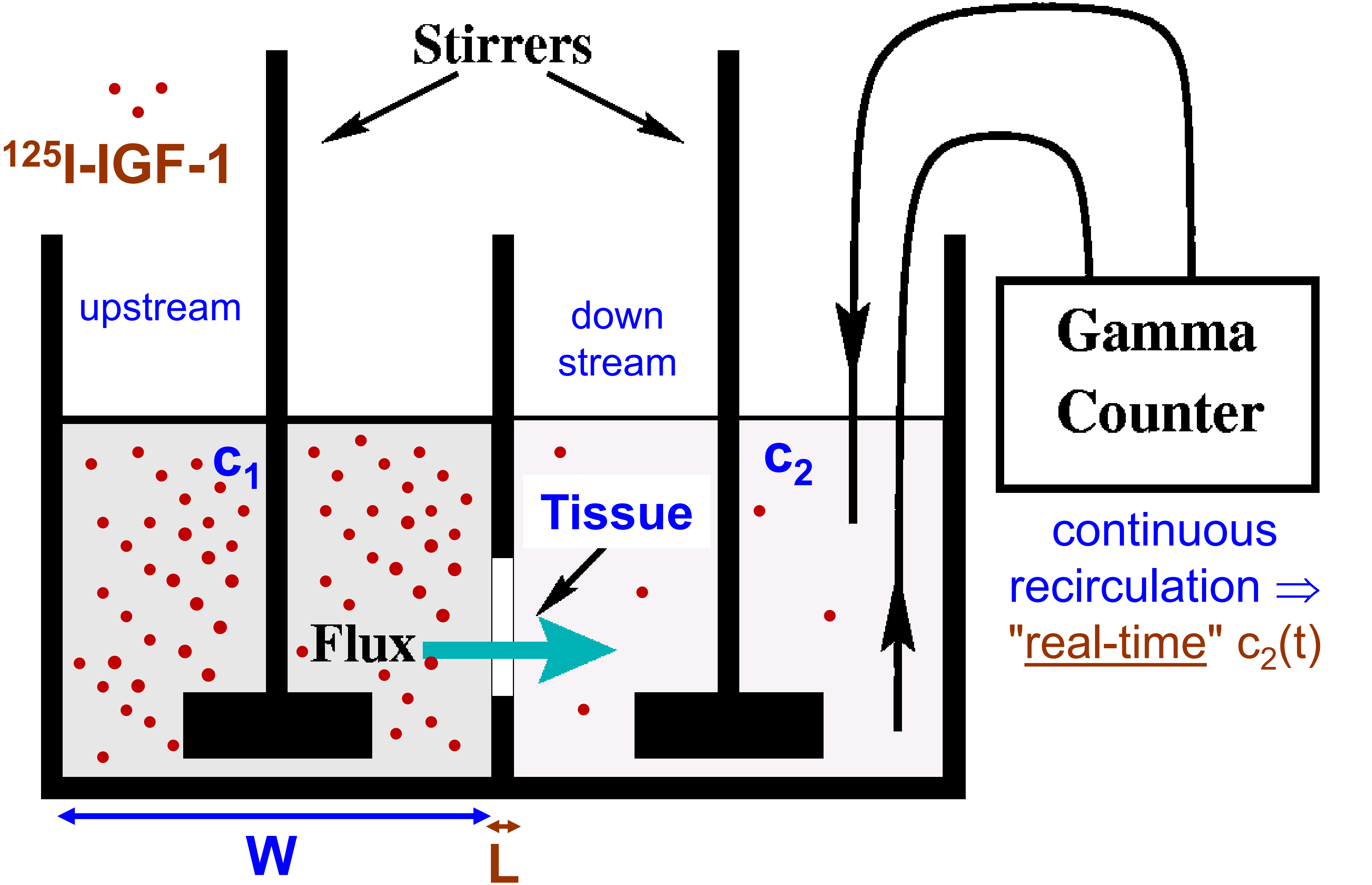
Purify ^{125}I-IGF-1

Sephadex G50 Gel Filtration Chromatography




TIME
SEQUENCE
[A]
Sample
Injection
[B]
Size
Separation
[C]
Large Solute
Eluted
[D]
Small Solute
Eluted
Solvent
Flow
Porous Gel
DETECTOR

Experimental Setup: Transport



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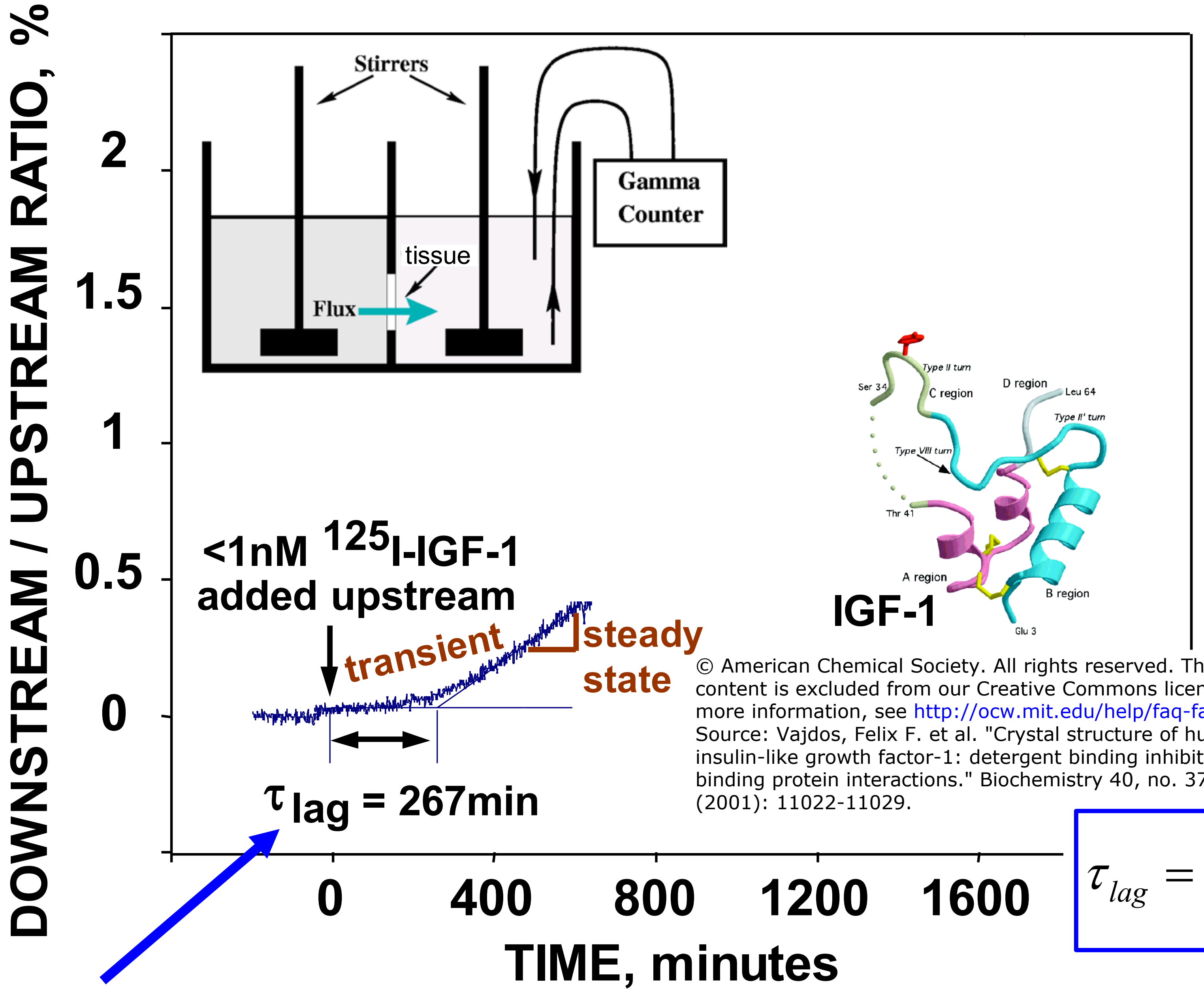

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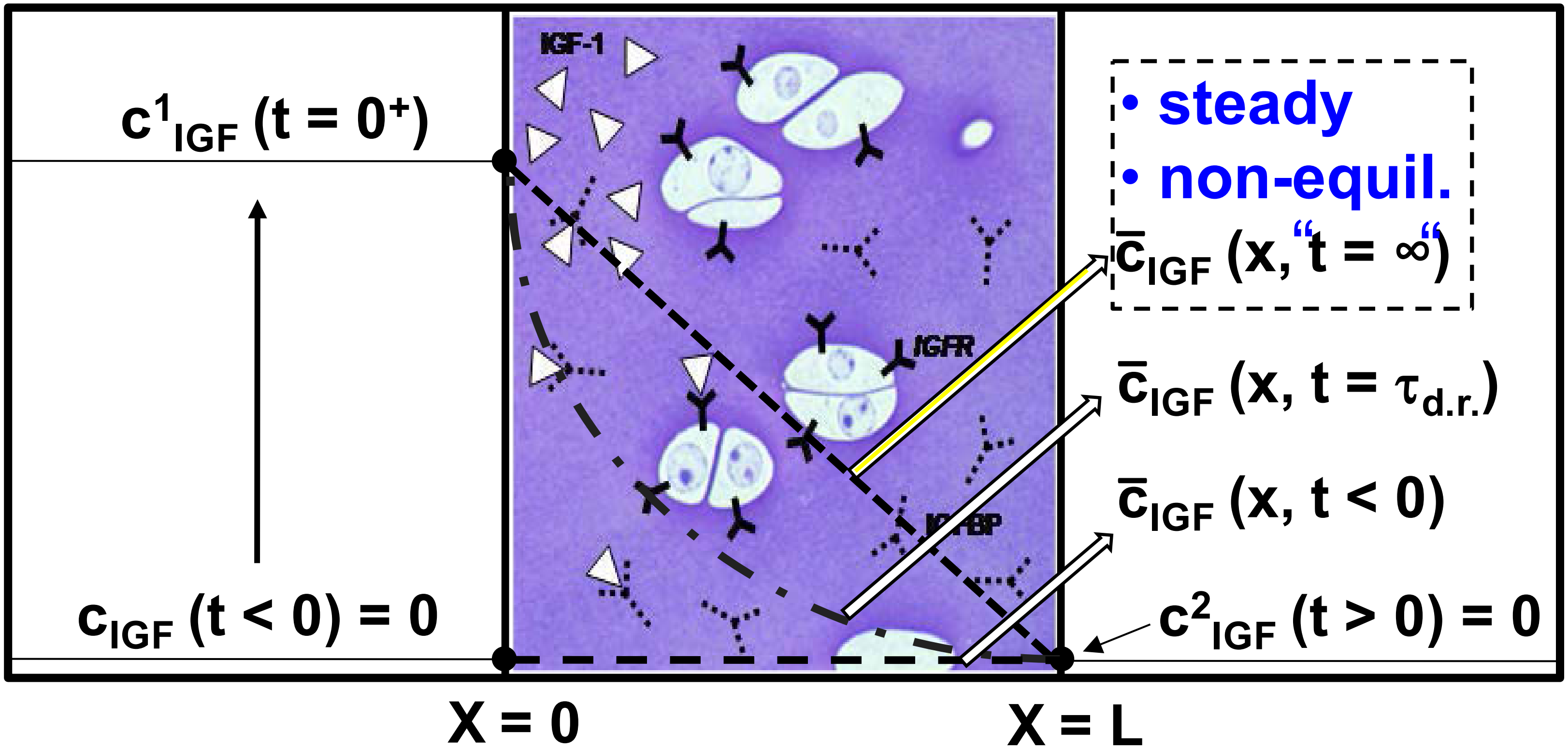
slow reaction, or slow diffusion compared to reaction???

Prob Set 2, Prob 1



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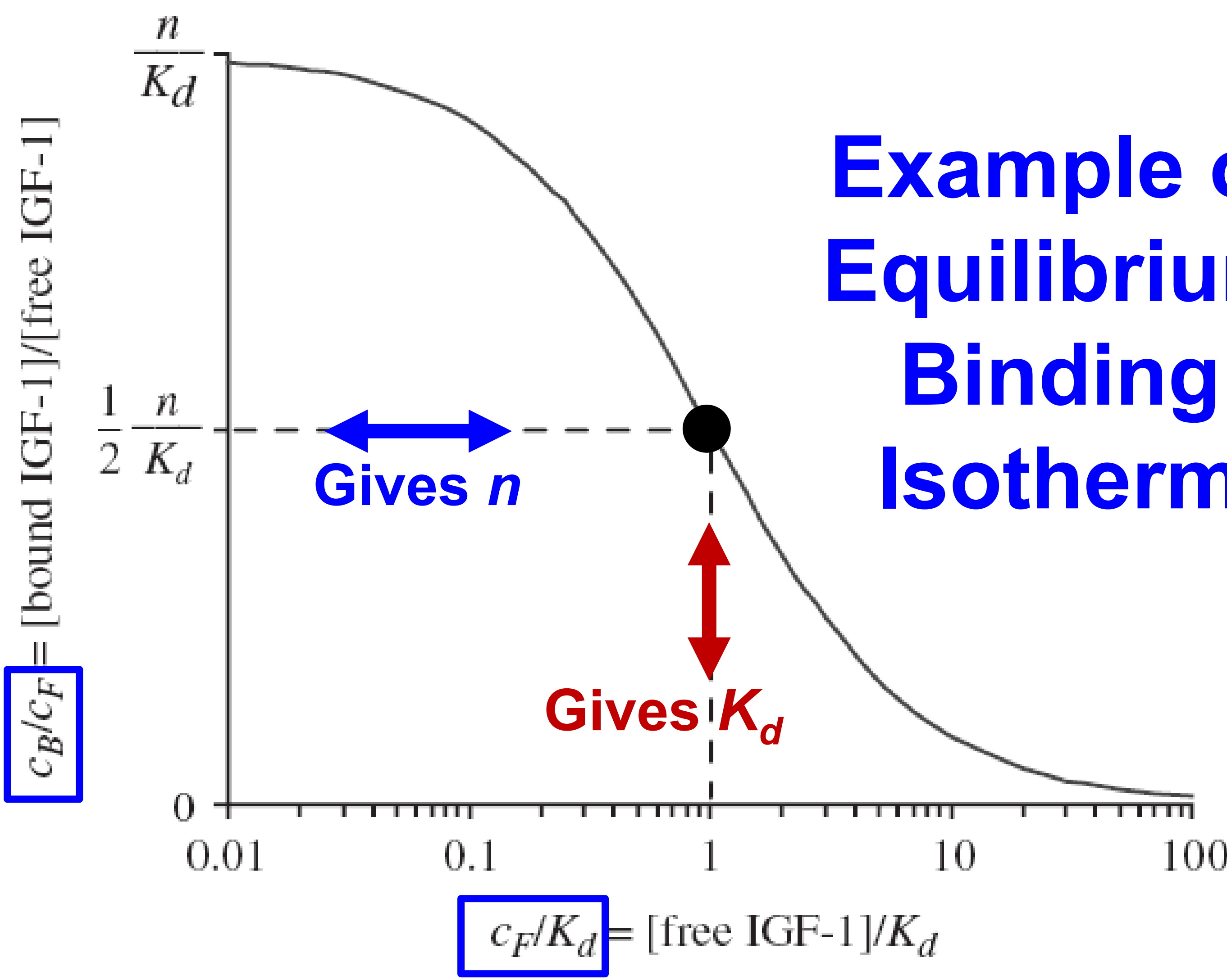
$$\tau_n = \frac{L^2}{n^2\pi^2 D_{\text{eff}}} \qquad \boxed{\tau_1 = \frac{L^2}{\pi^2 D_{\text{eff}}}} \quad (1.73)$$

Example of Equilibrium Binding Isotherm



(Bound IGF-1 / Free IGF-1) versus free IGF normalized to K_d