Term Paper Project:

Enzymatic Targeting of the Stroma Ablates Physical Barriers to Treatment of Pancreatic Ductal Adenocarcinoma

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Cancer Cell, 2012

Hyaluronan, fluid pressure, and stromal resistance in pancreas cancer

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British Journal of Cancer, 2013

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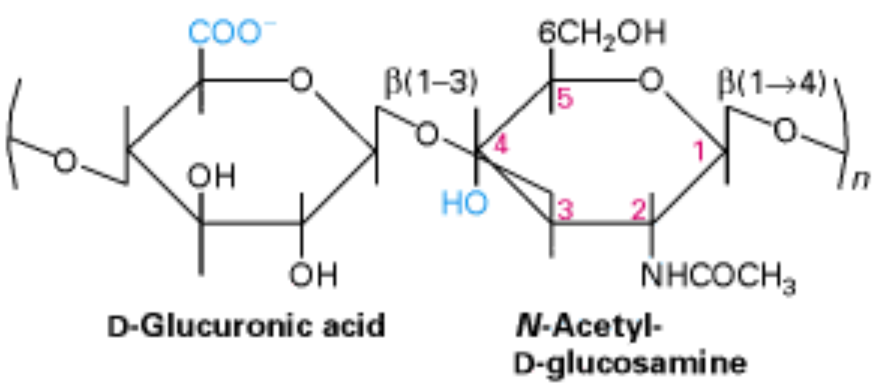
Source: Prof. Paolo Provenzano's website.

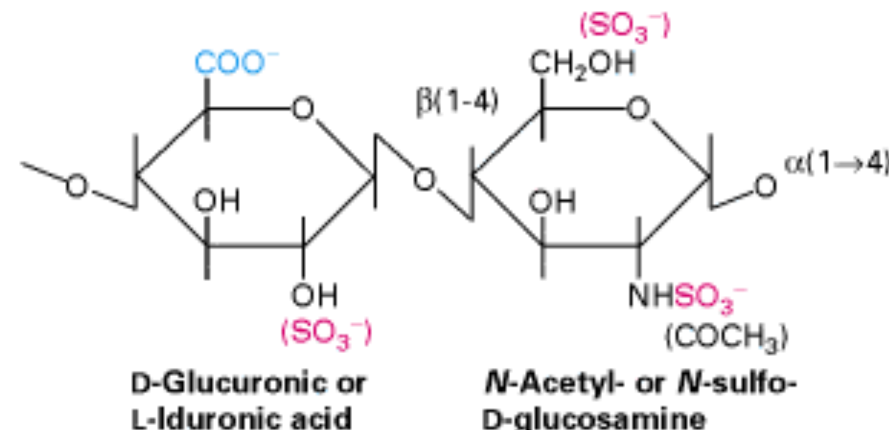
Family of glycosaminoglycans (GAGs):

Major components of the extra-cellular matrix of tissues and tumors

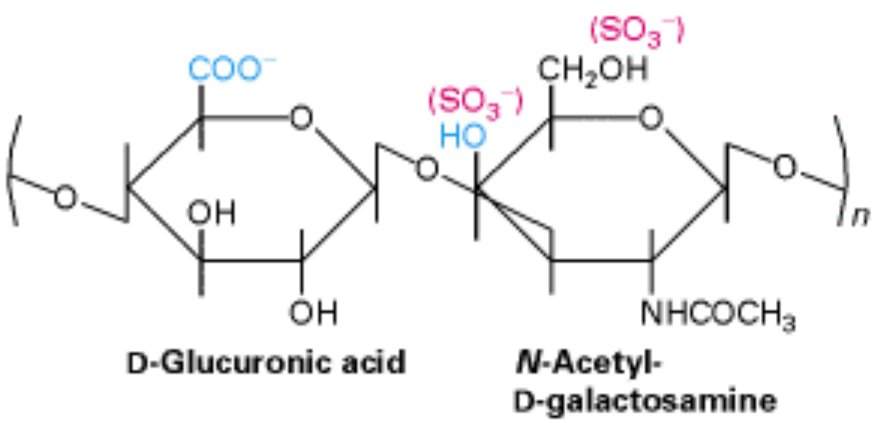
Hyaluronan (n < 50,000)

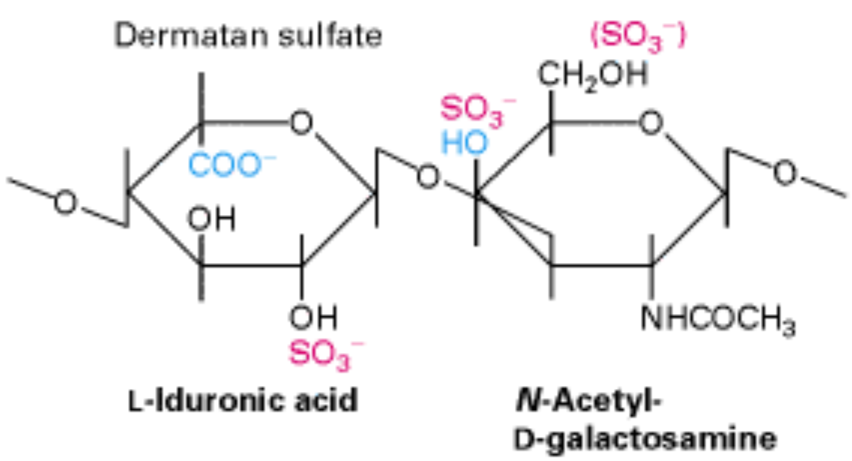


Heparan sulfate (n=15-30)

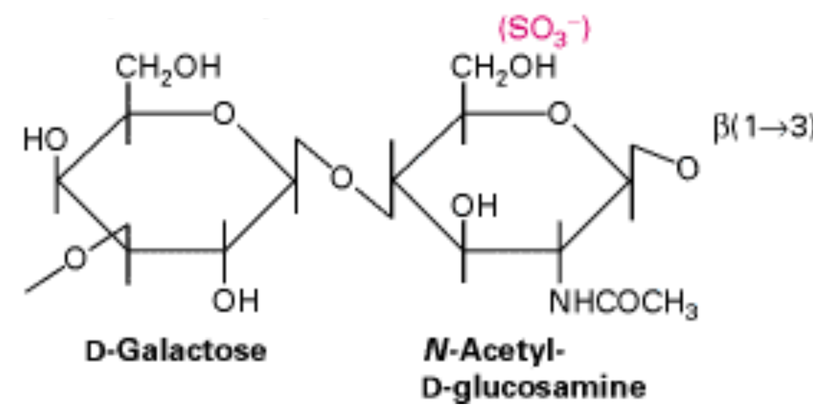


Chondroitin Sulfate (n<250)





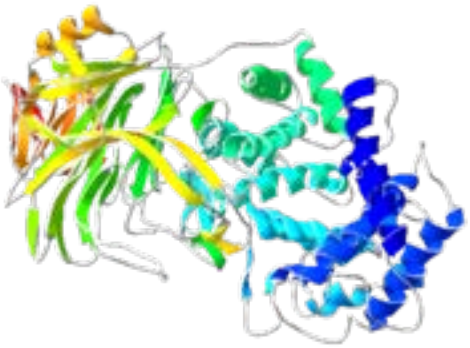
Karatan sulfate (n=20-40)



Hyaluronan synthesis and degradation

Text from "hyaluronan synthase" article on wikipedia removed due to copyright restrictions.

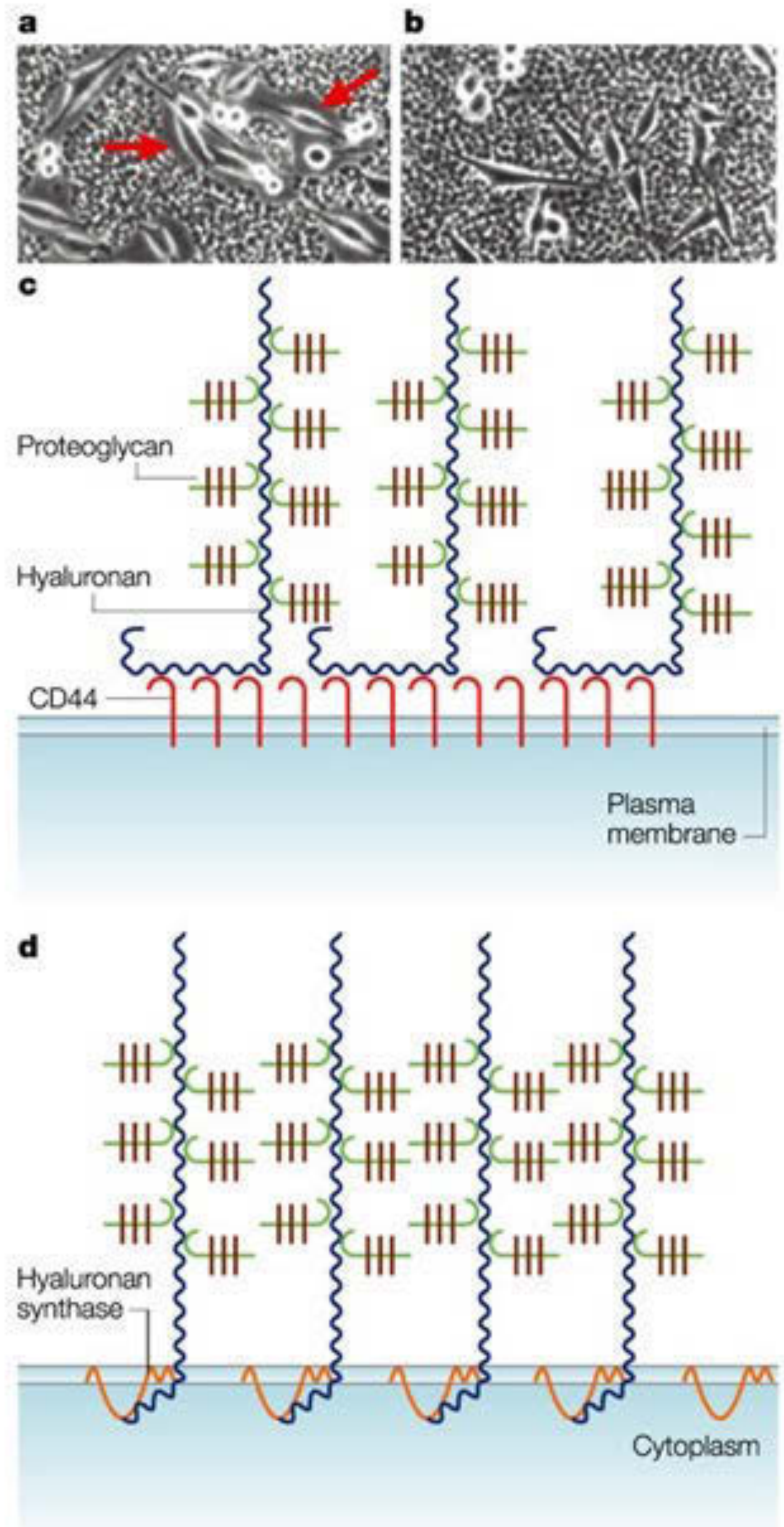
Text from "hyaluronidase" article on wikipedia removed due to copyright restrictions.



Hyaluronidase

Courtesy of Jag123 on wikipedia; image in the public domain.

pericellular "coat" +hyaluronidase



Nature Reviews Cancer 4, 528 (2004)

Courtesy of Macmillan Publishers Limited. Used with permission.
Source: Toole, Bryan P. "Hyaluronan: from extracellular glue to pericellular cue." Nature Reviews Cancer 4, no. 7 (2004): 528-539.

Cancer Cell

Enzymatic Therapy for Pancreas Cancer

http://www.halozyme.com/Products-And-Pipeline/Pipeline/PEGPH20/

P_i, interstitial fluid pressure

P_v, intravascular fluid pressure

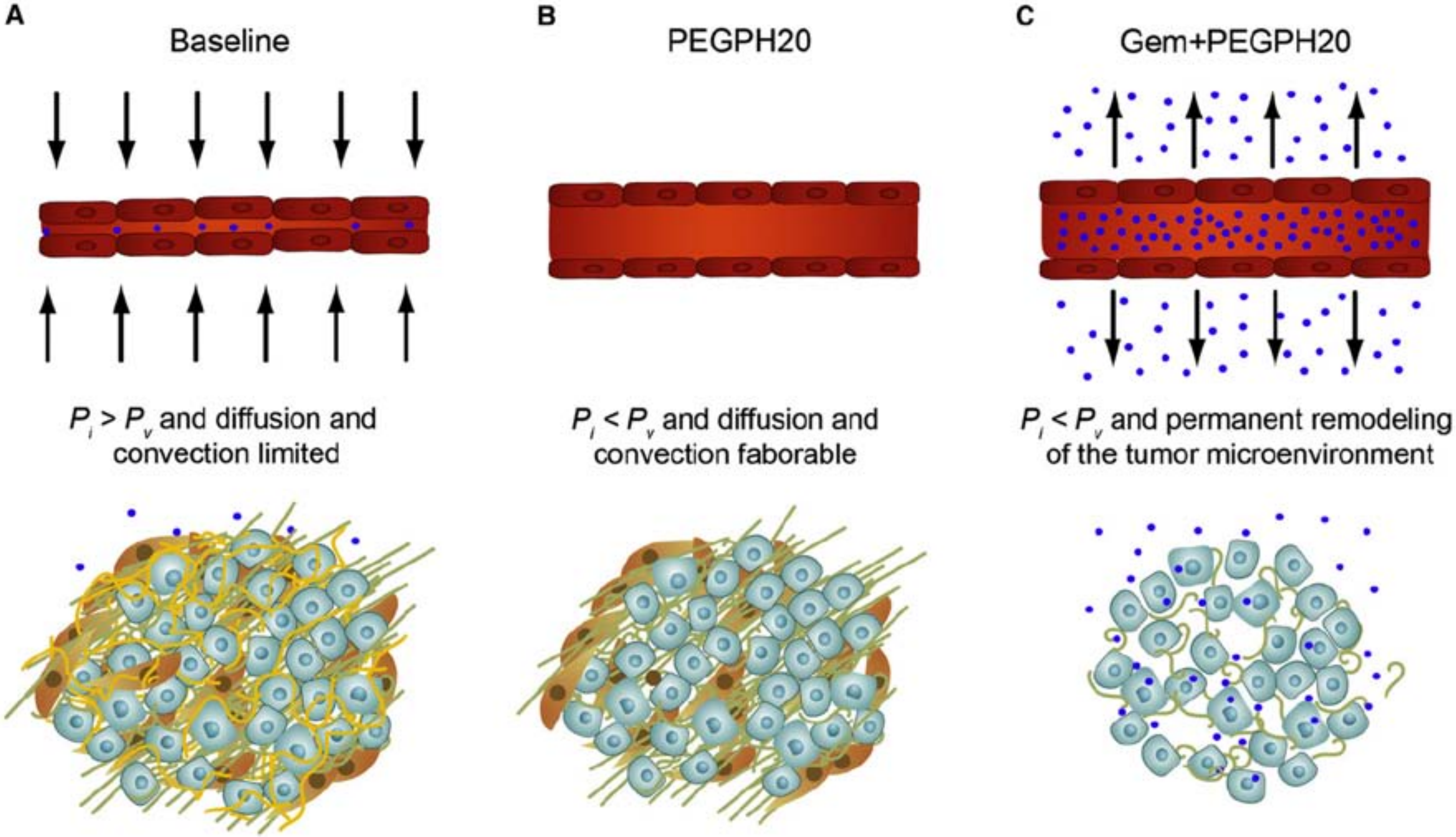


Figure 7. Altering Physicomechanics and Remodeling the Stroma in PDA to Therapeutic Advantage

(A) Intratumoral mechanics in PDA impede diffusion and convection of small molecules.

(B) Enzymatic degradation of stromal HA decreases IFP and relieves physical constraints on small molecule perfusion, which can reconstitute in the absence of additional therapy.

(C) Combined enzymatic and cytotoxic therapy permanently remodels the tumor microenvironment to favor the delivery and distribution of small molecules. Blue spheres represent chemotherapy molecules, vessels are shown in red, carcinoma cells in light blue, activated PSC in brown, collagen in green, and HA in yellow. P_i, interstitial fluid pressure; P_v, intravascular fluid pressure. See text for details.

Source: Provenzano, Paolo P. et al. "Enzymatic targeting of the stroma ablates physical barriers to treatment of pancreatic ductal adenocarcinoma." Cancer Cell 21, no. 3 (2012): 418-429.

Disagreement regarding the mechanism of action

Compression of Pancreatic Tumor Blood Vessels by Hyaluronan Is Caused by Solid Stress and Not Interstitial Fluid Pressure

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(Chauhan et al., 2013). Thus, we concur that PEGPH20 has immense promise for PDA, and we hope that this correspondence clarifies its mechanism.

Cancer Cell, 2014

Response to Chauhan et al.: Interstitial Pressure and Vascular Collapse in Pancreas Cancer—Fluids and Solids, Measurement and Meaning

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http://dx.doi.org/10.1016/j.ccr.2014.06.004

Chauhan et al. suggest that vascular collapse and hypoperfusion in pancreatic ductal adenocarcinoma (PDA) are caused by solid stress (SS) (Chauhan et al., 2014) instead of the elevated interstitial fluid pressure (IFP) associated with high extravascular concentrations of hyaluronan (Provenzano et al., 2012). We appreciate their attention to our work and the opportunity to clarify underlying mechanisms.

Cancer Cell, 2014

Your paper is to be no more than 20 pages in length, double spaced, including any pasted-in figures, graphs, etc. that you may wish to generate, as well as a bibliography listing any additional references that you may wish to quote or consult.

Teams: ***Each paper will represent the combined efforts of a team of 3 people***.

Suggested Approach: You should first read the paper as if you were asked by a journal editor to provide a review of the manuscript. In such a case, you would first list the strengths and weaknesses of the paper. For instructions on how to write an effective review, consult the following resources:

http://www.molbiocell.org/content/22/5/525.full
http://www.jci.org/articles/view/39424

Your paper should include:

(1) A Background section (length ~ 1-2 pages) that summarizes the *biological problem* being addressed, its relevance and/or importance to basic biology or physiology or human health.

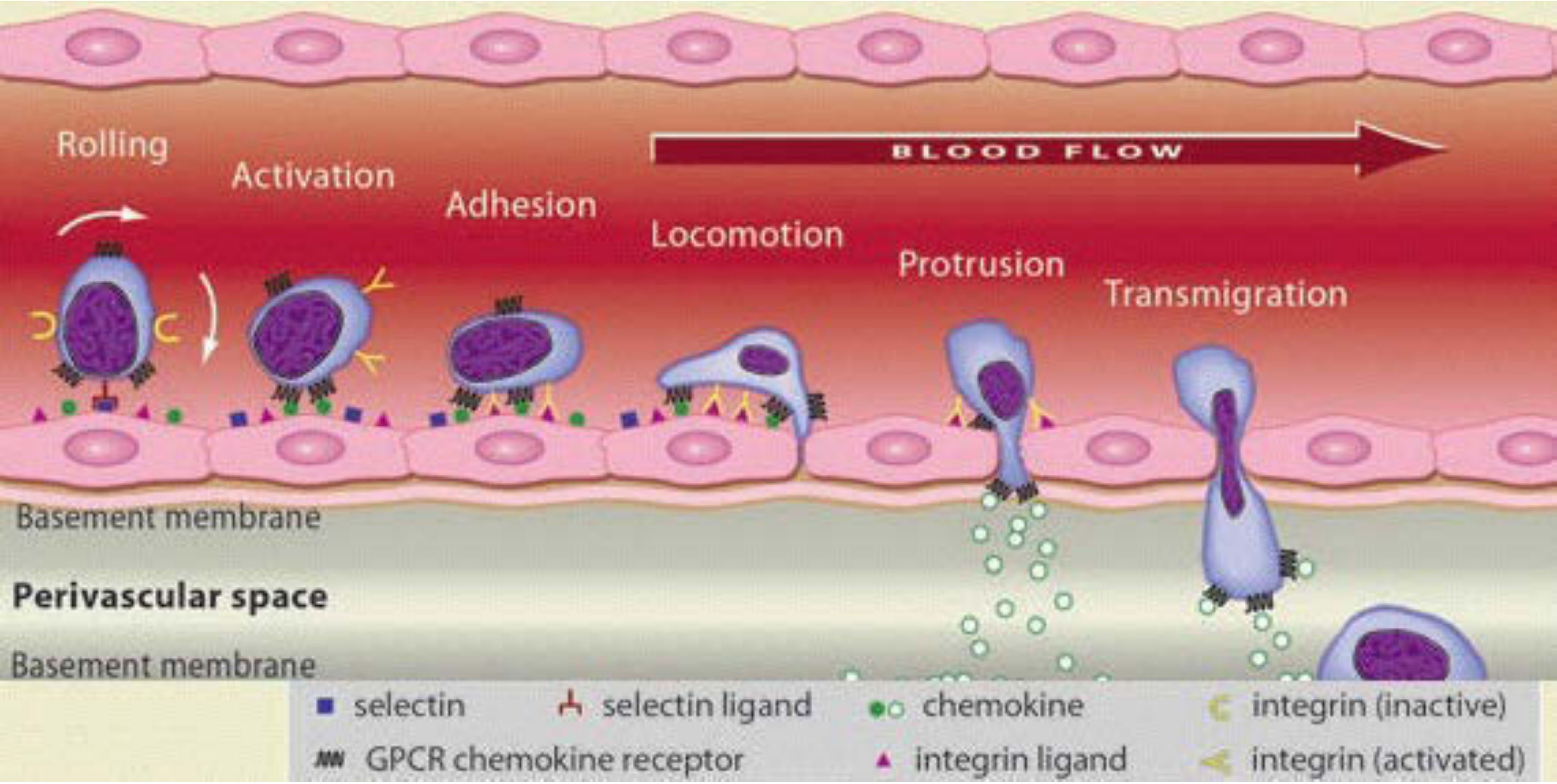
(2) A Summary of the experimental data: first, describe the approach and the general methods used; then give your opinion of the strengths and weaknesses of the approach and experimental methods; are there any fatal flaws? If so, what?

(3) Outline the controversy surrounding the authors' proposed mechanisms by which hyaluronidase treatment "works": Is there a model that has been proposed to explain the experimental data? If not, can you propose a model and additional experiments to test your hypotheses and explain the results?

(4) Improvements: Do you think the paper can/should be modified or improved? How so? Are there additional analyses that you can propose and/or carry out that would lead to a more substantial conclusion?

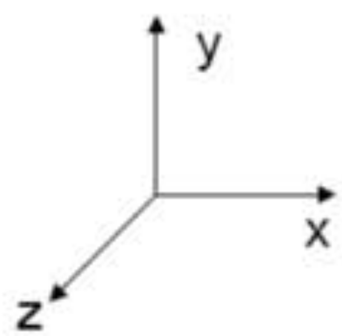
(5) Your summary recommendation: If you received this document from the editor of the journal as a manuscript for a review, what would be your recommendation?

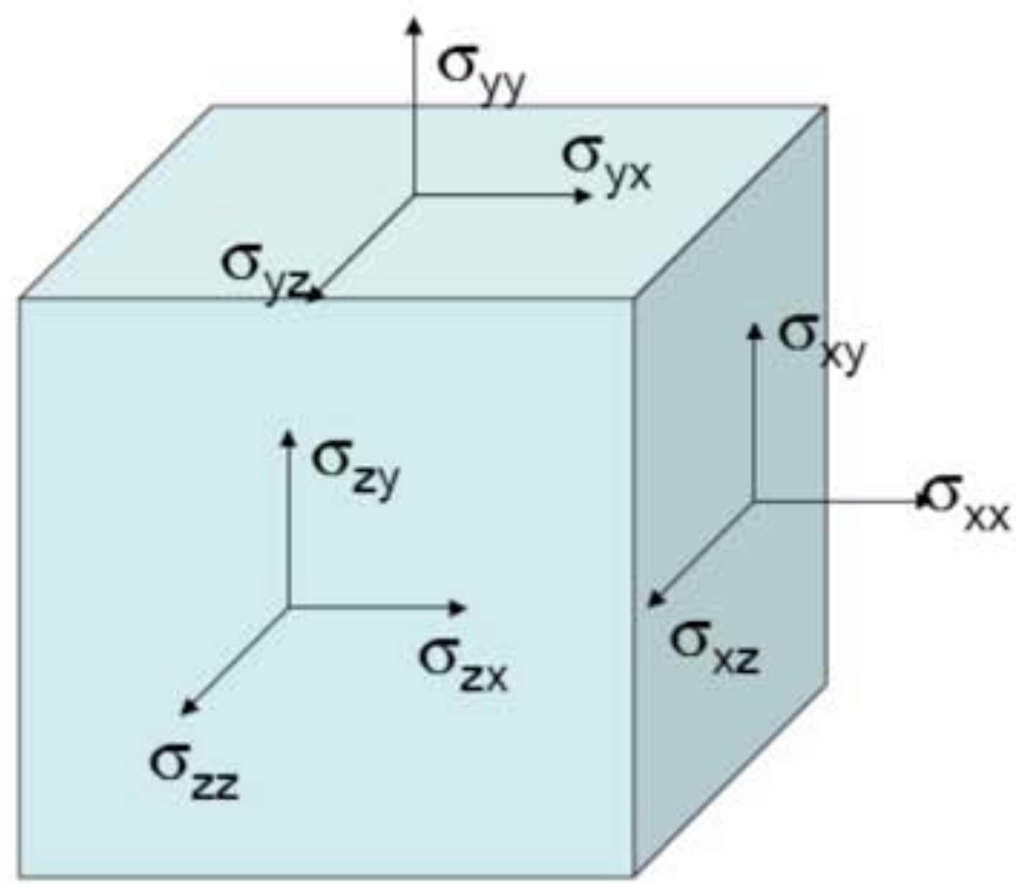
Leukocyte rolling, adhesion, and extravasation



Source: Man, Shumei, Eroboghene E. Ubogu, and Richard M. Ransohoff. "Inflammatory cell migration into the central nervous system: a few new twists on an old tale." Brain Pathology 17, no. 2 (2007): 243-250.

Stress Tensor: Surface Forces on a Fluid Element





$$\sigma_{ij} = \begin{pmatrix} \sigma_{xx} & \sigma_{xy} & \sigma_{xz} \\ \sigma_{yx} & \sigma_{yy} & \sigma_{yz} \\ \sigma_{zx} & \sigma_{zy} & \sigma_{zz} \end{pmatrix}$$

$$\sigma_{ij} = \sigma_{ji}$$

Newtonian Fluids and Viscosity

$$\tau = \mu \frac{du}{dy}$$

Figure of laminar shear in a fluid from "Viscosity" article on wikipedia removed due to copyright restrictions.

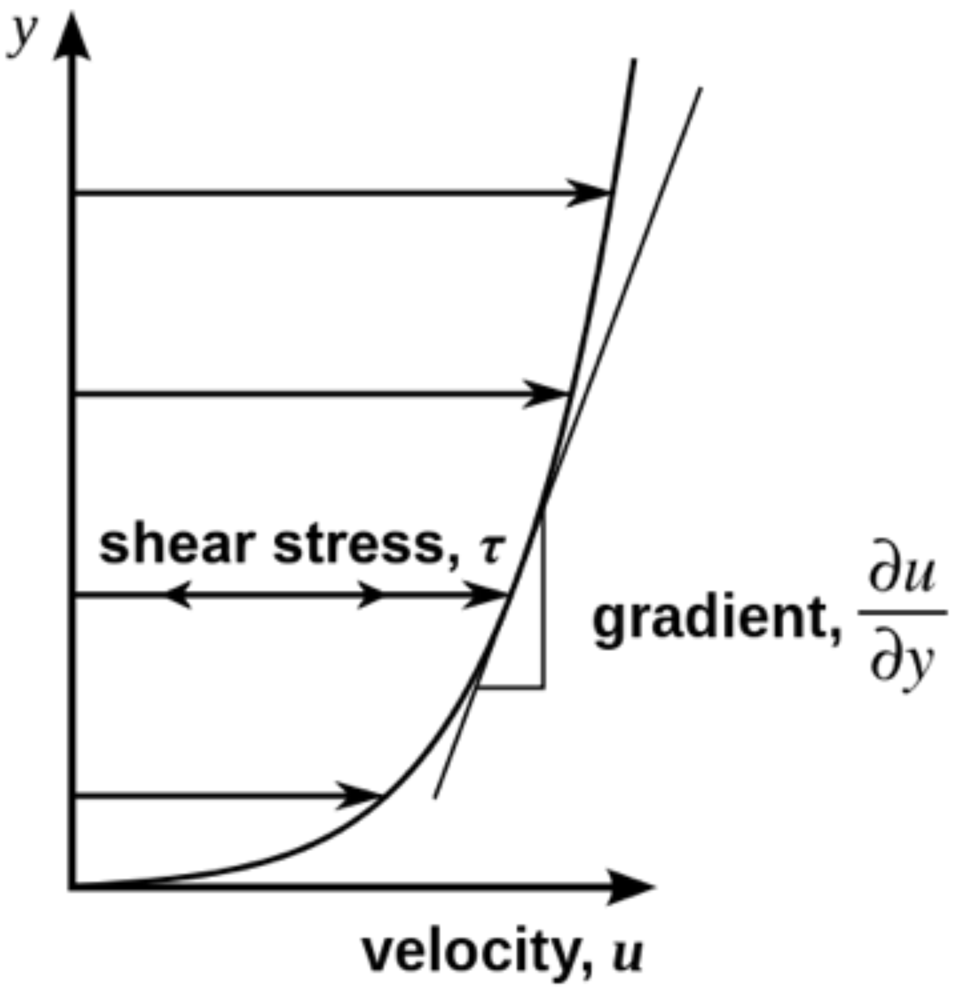
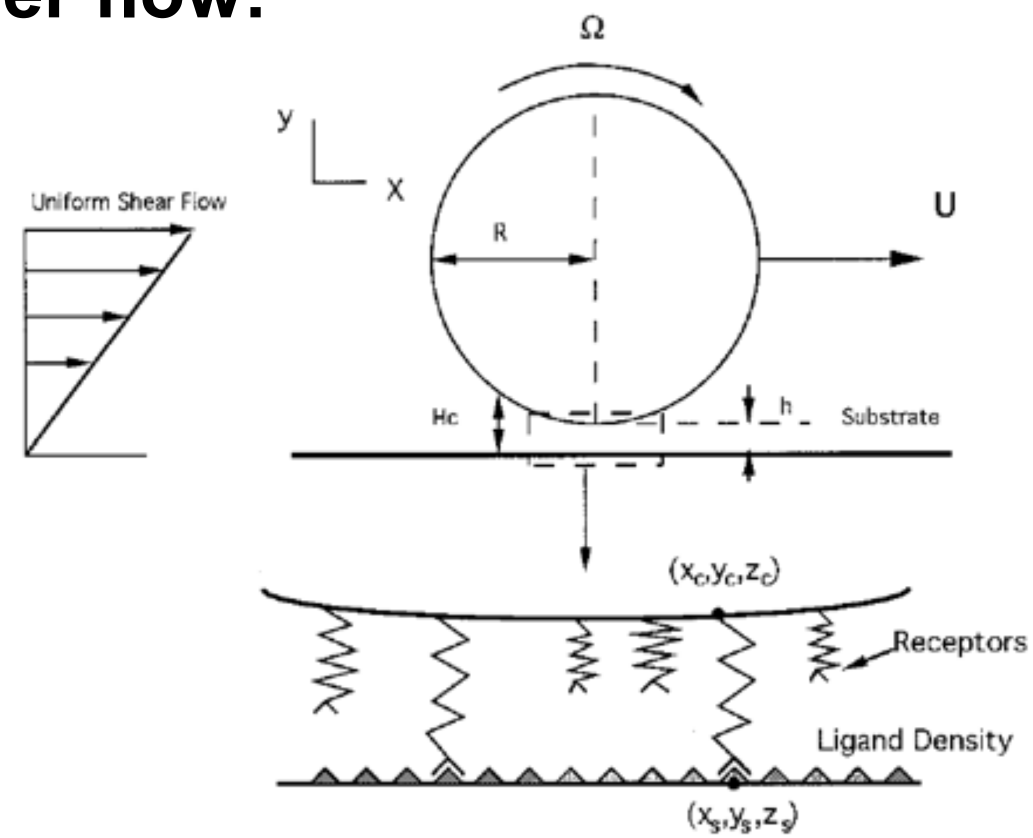


Image in the public domain.

“The state diagram for cell adhesion under flow: Leukocyte rolling & firm adhesion”



Bell model:

$$k_r = k_r^o \exp(\gamma f / k_B T)$$

bond rupture parameter — force-free dissociation constant

Table 2. Bell model parameters

Receptor–ligand pair (ref.)	γ, Å	k_r^o, s^{-1}
E-selectin–neutrophil (33)	0.31	0.7
E-selectin–neutrophil (34)	0.18	2.6
P-selectin–neutrophil (21)	0.40	0.93
P-selectin–neutrophil (34)	0.39	2.4
P-selectin–PSGL-1 (23)	2.5	0.022
P-selectin–PSGL-1 (35)	0.29	1.1
P-selectin mutant–PSGL-1 (35)	0.24	1.8
P-selectin mutant–PSGL-1 (35)	0.33	1.7
P-selectin mutant–PSGL-1 (35)	0.42	1.6
L-selectin–neutrophil (36)	0.24	7.0
L-selectin–neutrophil (34)	1.11	2.8
L-selectin–PSGL-1 (35)	0.16	8.6
L-selectin mutant–PSGL-1 (35)	0.15	12.7
L-selectin mutant–PSGL-1 (35)	0.12	17.3
L-selectin mutant–PSGL-1 (35)	0.11	18.3
PNAd–neutrophil (33)	0.20	6.8
PNAd–neutrophil (34)	0.59	3.8
Streptavidin–biotin $r_f < 10^4$ pN·s^{-1} (22)	5.1	0.013
Streptavidin–biotin $r_f > 10^4$ pN·s^{-1} (22)	1.0	26.9
Protein A–IgG (37)	7.3	0.12
PM-81 antibody–neutrophil (13)	0.88	2.0

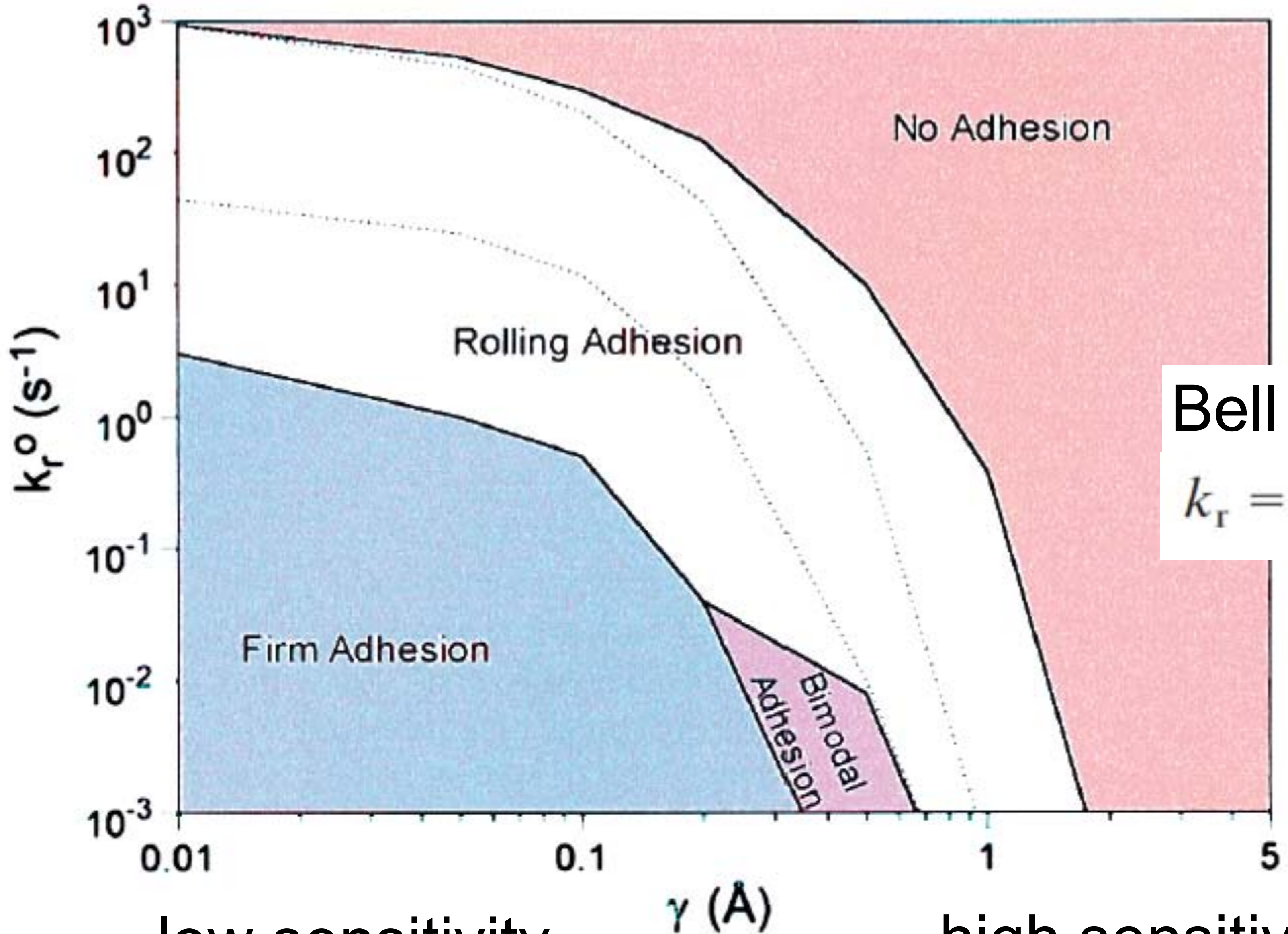
Table 1. Simulation parameters

Parameter	Definition	Value (ref.)
R_c	Cell radius	5.0 μm (14)
R_p	Receptor radius	1.0 nm (15)
N_r	Receptor number	25,000 (6)
N_L	Ligand density	3,600 cm^{-2} (6)
λ	Equilibrium bond length	20 nm (15)
σ	Spring constant	100 dyne·cm^{-1} (30)
μ	Viscosity	0.01 g·cm^{-1}·s^{-1}
G	Shear rate	100 s^{-1}
H_c	Cut-off length for formation	40 nm
T	Temperature	310 K
k_f	Association rate	84.0 s^{-1}

Hammer+ *PNAS* 2000

fast dissociation rate

slow dissociation rate



Bell model:

$$k_r = k_r^o \exp(\gamma f / k_B T)$$

low sensitivity to force

high sensitivity to force

Fig. 5. The state diagram with shear rate ranging from 30 to 400 s^{-1}. The dotted curves indicate the boundaries of the rolling state at shear rate = 100 s^{-1}. The rolling adhesion area represents the region of parameter space where rolling motion occurs over some part of the shear rate range from 30 to 400 s^{-1}. The no adhesion regime indicates that cell rolling velocity is always larger than $0.5V_H$ even when $G = 30\ s^{-1}$. The firm adhesion zone indicates that cells remain motionless even when $G = 400\ s^{-1}$. In the bimodal adhesion regime cells display either firm adhesion or no adhesion, without displaying rolling, as the applied shear rate is altered from 100 s^{-1} to 400 s^{-1}.

Hammer+ *PNAS* 2000