hello my name is Ben my from the

and uh I will talk today about the

pharmacokinetic and pharmacodynamics of

therapeutic proteins now with part

two the goals of this section are to

understand the distribution Behavior of

diptic proteins in the human body after

Administration into the vascular

system to appreciate the main processes

involved in the tissue penetration of

therapidic

proteins to recognize the need for

Parental administration of therapetic

proteins and to acknowledge the

processes determining absorption and

bioavailability after subcutaneous

administration of therapeutic proteins

in contrast to small molecule drugs

theraputic proteins are largely

distributed in the body by convective

exteris rather than

diffusion convective

extravasation

entails the following the fluid flux

from the vascular space into the

interstitial space and then its drainage

through the lymphatic system so theres

a Conant flow of fluid from the vascular

to the interstitial space and then into

the lymphatic system where its in

drained and ultimately reaches the

venous

bloodstream large therapeutic proteins

follow this fluid

flux they do this by either paracellular

or transcellular extravasation processes

through the endothelial cells lining the

blood vessels thats indicated here

where you have the trans cellular

process as well as the paracellular

process usually through pores between

the cells the more important process is

the paracellular

transfer dependent

on

the tissue and the endothal cells lining

this tissue there are more or less pores

available and the size of these pores

also changes in many tissues however the

transfer is restricted relative to the

transfer from the interstitial

space into the lymphatic system as the

lymphatic system or the the cells lining

the lymphatic vessels have many more

pores and larger pores so the influx

into the interstitial space is much more

restrictive as indicated by the smaller

errors here compared to the

outflux what that means or in other

words the uh lymphatic clearance is much

larger than the extravasation clearance

what that means is that the

concentrations in the interstitial space

always remain substantially lower than

the concentrations in the vascular space

as the influx is more restrictive than

the

outflux by that theraputic proteins are

largely confined to the vascular space

and concentrations outside of that

vascular space are substantially lower

throughout the bodies there are of

course exceptions to that in organs

where for example um the endothelial

lining is is nearly completely missing

or where there are a lot of uh pores

available for example in the liver

sinusoids where the exchange is uh much

less restrictive and by that of course

and the concentration in the vascular

space and into the in the interstial

space became become more

equal so convective exavation is driven

by the difference in convective uptake

into tissues and convective Al mination

via lymphatic

drainage um Unbound IGG concentration as

an example for this and remaining

concentration gradient are approximately

0 fold lower in many tissues compared

to

plasma the extravasation rate also

depends as I mentioned to uh on Regional

differences in the capillary structure

for example uh in those tissues with

leaky capillaries you have less of a

concentration difference between the

interstitial space and the plasma and

then of course you have disease states

where the uh

permeability uh of the endo theum may be

changed like inflammation and

angiogenesis uh where the local endium

becomes hyperpermeable to macro

molecules and by that also extravasation

is more

effective as I mentioned theres also

transcytotic extravasation through

transport through the endothelial cells

this is usually

facilitated via membrane vesicles that

are uh transported from one side of the

cell to the other and is usually

receptor mediated but overall in most

cases it constitutes a much lesser

degree to the overall distribution

process rather than the convective

extravasation through the pores as I

mentioned

previously distribution processes are

largely determined by molecular weight

size shape and charge and polarity of

the macromolecule so for example the for

those with high molecular weight theyre

usually confined to the vascular space

and to the lesser degree as I mentioned

to the interstitial space so what is

then the uh typical uh pharmacokinetic

Behavior after intervenous

Administration you usually get a bio

exponential concentration time profile

where the central volume of distribution

is equal to or only slightly larger than

the plasma volume so to liters and

the overall volume of distribution

remains limited uh for many therapeutic

proteins uh in the range between to 0

lit examples are uh provided here arrin

Alpha dartin ector place and tromo potin

as some examples that have a vol volume

of distribution at steady state between

0 uh 0 five and 0 L per

kilogram now if uh therapeutic parins

need to be administered and they would

be administered by the oral route then

they have uh no appreciable or buy

availability and that uh means that they

need to be administered by intravenous

administration either as infusion or

injection the main reason for that is

twofold one is that the gastrointestinal

tract has high proteas activity so its

the most efficient metabolism site for

uh proteins in the body for obviously uh

proteins that are taken off for for

nutritional

purposes and uh in addition to that

however theres also a low

permeability of large therapeutic

proteins through the

gastrointestinal mucosa that has been uh

shown uh in um humans that have been

given um Inhibitors of gastrointestinal

produce activity even with those

Inhibitors you do not have any

appreciable bio availability so theres

a low permeability through the GI mucosa

thats ultimately the main obstacle for

uh oral bioavailability of the apiic

proteins and thats really related to

the large molecular size uh uh molecular

weight and size of theraputic proteins

so the Alternatives that are then used

are as I mentioned either IV

Administration or subcutaneous

Administration subcutaneous

Administration especially popular for

self Administration shown on the right

side are two examples for that uh on the

top and a delum map uh single injection

pan or on the bottom a multiple

injection pan for uh a flex propan for

human grow

hormone alternative Administration

routes that are used for some diptic

proteins and have been explored is

internasal Administration as well as uh

ponary inhalation but again these routes

are more uh Niche Administration

Pathways the vast majority of theraputic

PRS is either given by intravenous

administration as injection or infusion

or uh by subcutaneous

Administration after subcutaneous

Administration into the subcutaneous

interstitial space as indicated here uh

the therapeutic protein has the

theoretically the ability to either be

taken up into the vascular

space clone on the left side or in

drained into the lymphatic system and

then undergoing lymphatic drainage and

ultimately entering uh the Venus

bloodstream

since therapeutic proteins follow the

fluid flux the convective uh

extravasation that has previous that I

have previously shown you they also
follow the same fluid flux when they are
administered uh by subcutaneous
injection into the interstitial space so
there is a preferential uptake of large
therapeutic proteins into the lymphatic
system and only a very minor uptake into
the
vascular
space that has substantial consequences
with regard to the rate and the extent
of absorption after subcutaneous
injection shown on the left side here is
a relationship between the uh percent of
the dose thats recovered in the
lymphatic
system versus the molecular weight and
whats shown on the left are two small
molecule drugs by Flo to this oxy urtin
and inin and then two small um proteins
and you can see that with increasing
molecular weight the lymph recovery in
percentage of the administered dose is
largely increasing
already uh reaching approximately 0
for interfere on Alpha

a you now imagine what happens if you

give an even larger theraputic protein

like an

uh abum fusion protein with 9

kilodalton or high or a monoclonal

antibody with approximately an0

kilodalton then

ultimately uh nearly all of the

administered dose will end up in the

lymphatic system and will not be uh

absorbed into blood capillaries so the

larger the molecular weight the higher

the percentage thats absorbed into the

lymphatic system and as I mentioned for

large theraputic prod like monoc

antibodies approximately 00 of the

absorbed of the of the administered dose

is absorbed into the lymphatic system so

what are the consequences of that the

first one is that um you have slow

absorption due to the much slower flow

rates in the lymphatic system compared

to the

bloodstream the second one is that you

have substantial presystemic metabolism

due to this long

residence time in the lymphatic system

since the transport is that slow uh

protein molecules can interact with

endothal cells as well as with fosic

cells especially concentrated in lymph

nodes where blood uh lymphatic vessels

drain to and by that they can undergo

metabolism and by that they never reach

the systemic

circulation uh when they are preem

mically degraded so theres substantial

presystemic metabolism through this

passage um through the lymphatic system

and this reduces the overall

bioavailability after subcutaneous

Administration for many therapeutic

proteins uh most monocon

antibodies have a uh subcutaneous buy

availability in the range of 0 to

they of course always exceptions to that

there are some that have higher bi

availability but for many you have a

substantial fraction of the administered

dose that under goes presystemic

metabolism before ever reaching the

systemic

circulation so in

summary theraputic proteins leave the

vascular space primarily via convective

extravasation rather than diffusion thus

the concentration in the intertial space

are usually substantially lower than in

the vascular

space thetic proteins are not by

available after all Administration and

usually have to be administered

parentally and absorption of theraputic

proteins after subcutaneous

Administration is largely facilitated by

the lymphatic system resulting in slow

and protracted absorption and reduced

sustain

by

availability this concludes section two

again to questions as for self

assessment um of the presented

material