we are honored to have dr jerry collins

dr collins associate director of the

developmental therapeutics program in

the division of cancer treatment and

diagnosis at the nci

he received his phd in 9 from the

university of pennsylvania and completed

a postdoctoral fellowship in clinical

pharmacology at johns hopkins

he has authored or coauthored over 00

papers in the field of clinical

pharmacology

primary emphasis in the area of

pharmacokinetics and pharmacodynamic

principles in the field of cancer

prior to his current position he spent

years at the fda

please enjoy todays lecture

my name is jerry collins

im here today to talk about

topics that are contained in chapters

and  of the textbook

my day job is that i lead the

developmental therapeutics program at

the national cancer institute

my background is that ive spent half of

my adult life at the national cancer

institute and half of my adult life at

the food and drug administration

neither of whom assumes responsibility

for anything that i might say tonight

chapter  was

written by bob dedrick who originally

joined me in sharing this but hes

retired left me his slides and ill have

to try to represent them as i can bob

dedrick

was a chemical engineer he was a

founding director of the chemical

engineering section here at nih and

just had a marvelous perspective about

the relationships between phenomena in

the physical chemical world

and phenomena in the biology world

so what do chemical engineers do well

one of the major things they do is they

make enormous quantities

of materials specialty chemicals bulk

chemicals kilograms in these large

chemical plants

and how do they do that

well they start out figuring out how to

synthesize the molecule in test tubes

using milligram quantities

and so the process of going from

milligrams to kilograms which is at

least a million fold difference

is what chemical engineers call

scale up

and as bob thought about that process

his his lifelong training

his question is well whats it like in

biology

in biology we have these just within

mammals we have these tiny rodents

and we have these enormous animals

what are the similarities and

differences how do you get from small

creatures to large creatures

what are the similarities

and what are the differences

in fact one of bobs favorite sayings is

engineers look for similarities

biologists

look for differences and most of the

people who signed up for this course are

are of course biologists but

well try to give bob a chance to uh

convince us of the role of

similarities so this is a lab tech in

building  and campus a little bit

earlier in time when you didnt have to

wear gloves all the time when you were

handling animals and so the mouse and

the rat clearly

have similarities you can see that they

look

sort of the same shape and different

from other mammals but its a tenfold

difference youre talking about a 0

gram mouse and a 0 gram rat

so what are the implications of that

size other other than uh

one needs more food to eat

and

you know more cage space

but bob didnt stop it there his other

hobby was that he was a photographer

so

sure enough he wandered down to the

washington zoo and took this picture

so the picture he convinced the

zookeeper who was happy to participate

in this experiment to stand next to the

elephants that the zoo keeper worked

with

and so compared to a rat

a human is 00 times larger

but

compared to

a human

a mouse is several hundred times larger

than a human at least in terms of body

weight so we just have this enormous

scale

just again just within the mammalian

kingdom in terms of um what size

processes were bobs a very curious

person

he knew how that worked in uh chemical

engineering and he wanted to learn and

contribute to that in

the world of drug distribution and

pharmacokinetics

so it turns out that

because theres such a wide variation in

body weight that biological processes

have to scale

they they do things differently they do

things at different rates at different

turnover

volumes at the small end of the scale

than the large end of the scale

and

0 years ago

adolf published this paper in science in

9

on allometry

and everybodys eyes glazed over and

said what why do i need to know anything

about elementary well adolfs simple

point was

even if you dont know

the fundamental underlying processes

that youre measuring whatever it is

temperature heart rate heart rate

amount of food intake

body surface area

theres an empiric relationship that

covers

all of those

diverse equations and thats this

equation in the middle of the slide

where the property

is equal to some constant times body

weight to the nth power

well thats all that it means it doesnt

mean that we know exactly why

a is one value and m is another value it

just means that as you as you look at

series of data across a wide range this

equation comes up over and over again

and for someone whos curious they would

say this cant be a coincidence in fact

this is very similar to the way chemical

plants are designed theres a scale up

from milligrams to kilograms that

follows a uh allometric allometriclike

like process

when you see these plots theyre a

little different from most of the

pharmacokinetic plots youve seen in

this course in that its a log log plot

both the y and the xaxis are logarithms

its the only way you can squeeze all

the data from

a diverse mammalian species onto the

same graph

and this the two squiggly lines are just

showing you what happens when the

property is directly proportional to

body weight where the exponent is

versus when its 0 which

is sort of a magic number in a llama

tree

good news is we wont talk about why

its a magic number so here here is uh

heat production

so

all mammalian species are warmblooded

animals theyre aiming for a particular

target

body temperature how do they achieve

that they achieve that

primarily except for us they achieve it

primarily by adjusting their rate of

metabolism adjusting their their heat

output

and if you plot on the bottom everything

from a mouse to an elephant over you

count them half a dozen logs

and then you look at the heat production

on the yaxis

it it keeps coming up again no matter

what property you are looking at

um the allometric equation the loglog

plot is important

so this is the way bobs thought process

works he says well there must be a lot

of similarities there must be a way we

can put this together in a way that

would be useful in drug distribution and

pharmacokinetics

so

more recently a mere 0 years ago bob

and his colleague collaborator ken

bischoff invented something called

physiologic based pharmacokinetics

now largely pharmacokinetics today

remains

empiric based on one compartment and two

compartments

interpretations but there are a number

of questions that are much better

answered or answered in more detail if

you think about the underlying

biology the underlying physiology

so lets go through a couple of answers

one of the one of the reasons i like

bobs uh

publication on cytoscene arabinoside rsc

is that he scaled the size of the boxes

to represent the volumes of the

compartments

and most of the empiric models that i

see all the boxes are the same size

thats okay

but it sort of gives you an idea of how

important the muscle mass is we rarely

think about muscle mass in terms of the

implications of pharmacokinetics and

pharmacodynamics but its the largest

reservoir in many cases of where the

drug goes

ah the part youve been waiting for a

mass balance equation particularly a

differential equation

all thats meant by a mass balance

equation is take a look at an organ or

an organism

figure out everything that goes in and

comes out think about whats happening

in the end and write it down

and see if you learn anything

about the processes and about that organ

and about that organism so what are

those things for metabolism theyre

things like vmax and km

for transport that starts with just

blood flow bringing it around the body

various flow rates q and then for other

elimination processes we talk a lot

about clearance cl

lets see what we learned from that so

this is one of the this is is the model

that ive been talking about bobs model

in uh for heresy

and this is his simulation

for

area c data at the bottom the bottom

line and the sum of are c plus area u

its metabolite at the top which is

important because the assay a lot of

people used in those days was total

radioactivity which is mostly measuring

the metabolite

so do those lines fit those data points

i think everybody in this room could

probably do a better job

fitting those data points to a

curvilinear line but bob didnt fit

those he predicted those

curves

he simulated the behavior based on all

those micro constants vmax km blood flow

and total clearance and then taken in

that context its pretty remarkable that

you get anywhere near

the

empiric data on pharmacokinetics

thats one species

one drug does that generalize again

bobs interested in principles that you

know go across a a wide landscape

so this is another cancer drug um

five flurry uracil

and

over the years data were collected in uh

dogs humans rat and mouse

and they all look a bit different

uh when plotted when coplotted on the

same graph where all youve done is

normalize the yaxis by uh by the dose

wonder why that is i wonder what whats

happening there can the same structural

pharmacokinetic model

predict the behavior for four different

species

if you know the differences in the in

the micrograde constants

and sure enough you can do that but a

more important or more interesting

question arose is

you know its not just size that changes

across mammalian kingdom its also other

properties like time

heart rates uh are radically different

across uh

species

lifespan is radically different and it

seems like

each species has its own time clock

and can you correct for that in trying

to understand differences across species

well

bob is far too humble to have called

this a dedric plot but

core and colleagues published this in

the

late 90s in which they named it after

bob in which all they did

was scale the time axis by body weight

and the concentrations all fall on the

same line

okay

in the grand scheme of things what does

that mean

again the fundamental message over and

over again is

you can find similarities even when

there appears to be a lot of differences

how hard is it to get those data to do

those simulations

well in the metabolism lectures uh in

back in the fall you heard some talk

about doing hepatocytes and microsomes

and various ways of

looking at metabolism

of drugs in the body so this is a set of

i dont know  drugs that was published

by

brian houston

in

in the earlier in the 90s in which he

looked at hepatocyte cultures okay you

could you can grow hepatocytes in

culture and this happens to be rats so

were switching from human which was

area c to rat now and instead of looking

one drug were looking at  different

drugs and what brian houston and his

colleagues did was create a

physiological pharmacokinetic model

which related

in vitro benchtop measurements and

hepatocyte systems to what that would

look in the whole body of a rat and then

in their laboratory they also collected

the whole body data pretty remarkable

curve if you look at any of those points

theres deviations but and theyre

sometimes theyre the most important

story but the key is were looking over

three orders of magnitude four orders of

magnitude and were seeing similarities

across a wide range despite the fact

that there are  radically different

structures that are are the drugs that

were

studied here

moving to human uh ito and colleagues uh

a few years later did the same

experiment that the houston lab did

um except they looked at humans and they

looked at a few more drugs in  i

didnt count them but maybe theres 0

of these

the interesting thing is that that

straight line falls apart as you get

very low

and as you get very high it looks very

similar why is that

well

if youre interested in similarities you

focus on the right half if youre

interested in differences you folk on

the left both are important if we go

back

to what what was the fundamental rate of

clearance in the rat

the curve ends at 0

in terms of clearance units on the

yaxis

whereas

in humans

its tails off at 0 what does that

mean there are other things in the body

besides the liver that account for how a

drug is biotransformed and excreted from

from the from the body so in general you

would not expect metabolism by the liver

alone to do it

it works in the rat because the rat is

so incredibly efficient at transforming

drugs relative to humans

so when humans

have drugs that have low clearances

then you begin to see to parse out this

tail on the left side of the graph which

shows the nonhepatic effect so again

you learn something from similarities

you learn something from differences

the last thing i i want to say of course

ive already said that

engineers look for similarities

biologists look for

differences

but both have in common

the fact that they collect a lot of data

in the laboratory and in other systems

and they want to use those data to

predict or extrapolate or scale up

from micro or many systems to larger

scale apparatus or larger scale animals

and so

always the engineer bob says that

biologists are

have a strong

interest in similarity just like

engineers do

all right lets transition away so so in

summary bobs idea and approach this is

to relate the things that he learned in

the physical chemical world the things

that are important in the biological

world particularly for uh for drug drug

development

and that was very helpful in

stimulating such areas as physiologic

based pharmacokinetics

which

took 0 years before about 0 years ago

it started to go into the mainstream in

in clinical pharmacokinetics so some

ideas take longer than others

what are we doing here at nih well

on about that same time frame about 0

years ago

nih started to think about reinventing

portions of it and the nih roadmap was

one of the mechanisms for doing that

and one of the priorities in terms of

rethinking some of the missions of nih

was reengineering the clinical research

enterprise

nih is always and forever will be known

for its basic research thats thats the

strength but since the basic research is

supposed to lead to some

payback later on in terms of the

clinical domain perhaps a little bit of

thinking in that area is is would be

useful

one of the things that came out of that

process was a creation of a new

institute or center the national center

for advancing translational sciences

whose mission statement says

they would like to speed the delivery of

drugs diagnostics and devices to

patients

its not that the folks that and cats

are in building one at nih think that

basic research is no longer important it

just means that we need to pay a little

bit more attention and we need to have a

critical mass

in terms of

the practical aspects of drugs

diagnostics and

devices

across the nih campus in various

institutes

the institutes have had small

therapeutics development or diagnostics

development programs for a long time

most of them dont have a critical mass

but they they they do perform a role

within within those institutes so it

wasnt

a completely out of the box idea it was

just more like shining the spotlight on

it

now

in the program that i lead developmental

therapeutics we do this with a much

larger

mission so

lets do the math 0 years ago

congress passed a law that mandated nci

to

figure out how to discover and develop

new therapeutics for cancer

if you think the landscape is difficult

for cancer therapeutics today 0 years

ago it was even more miserable

and congress said lets do something

about it there may be a parallel system

going on in the current political

climate but

were government employees and dont

talk about politics in any event our

website dtpcancergov

is the program that i lead and our major

pipeline is called nextcancergov

and the commercial

so chapter  is about first in human

studies which is an area that i spent

most of most of my life most of my

professionalized working on

i am also like bob a chemical engineer

by training but went into a postdoctoral

fellowship in clinical pharmacology

showed up here at the nih and um

i

spend just a lot of my time thinking

about the interface between

pre clinical and nonclinical studies

and

the early clinical studies statisticians

by and large design

pivotal phase  trials they do a far

better job than i ever would but im

interested in that interface between

the last of the preclinical studies and

the early clinical studies so over the

last two weeks ed sauceville and chris

takimoto have been trying to line you up

to think about the transition between

the late stages the transition between

the late stages of preclinical

development and how that influences the

earliest earliest clinical phases and

you can find in any textbook or review

article a diagram like this

and it is a nice model system to think

about but it certainly doesnt reflect

the way all trials are done increasingly

today

folks will say ive seen some really

exciting results

in a tiny number of patients in first in

human phase  studies

im going to make a large gamble and go

to an incredibly expensive large

complicated phase  study

thats a big gamble

the success rate is relatively low but

when it turns out you gain years almost

a decade in some cases

and you advance an effective therapy

into the clinic

but its a big gamble when you go

outside this paradigm similarly

drug gets

does okay in phase one from a safety

perspective gets to phase two and it

looks like it has this little problem

that it doesnt have much activity

and so theres a panic

and you certainly dont want to go

directly to phase three just because you

finished your phase two

if the result of your phase two is you

didnt find much activity so you throw

it back to the lab and you say fix this

get me a similar molecule that actually

has that activity so this is the real

world theres a lot of back and forth a

lot of iterative processes until you get

to the clinic

this slide just talks about the

contemporary trend to reengineering

first in human studies theres a lot of

new players cancer is a more attractive

target for many drug development

sponsors commercial and noncommercial

and just many things are coming together

to challenge the traditional way that

weve developed drugs are there some

better ways

well

i cant count the number of different

ways that you can do a first in human

study there are many of them

and my advice is not to get too attached

to any of them

this is an era in which theres enormous

flux in the philosophical underpinnings

of what a first in human study is is all

about and there are radical changes that

occur all the time

i would encourage you to think about the

fundamental principles that no matter

what algorithm you use for conducting a

first in human study

you have to do the scariest thing in

drug development

you have to pick the size of the first

dose in the first human being okay so

all the modeling all the preclinical

studies

all the genomics in the world

dont you know help help reassure you

that you have the right starting dose

but

you generally use a pretty large safety

factor you calculate what you think the

right dose will be in humans

and you put in a safety factor

and

you hope everything goes well if

everything goes well your reward is you

have a second problem

where do you go from the first dose the

first dose is rarely ever the right dose

the right dose in either one that does

it is basically the therapeutic index it

either doesnt have enough activity or

it has too much toxicity

so youre going to have to go somewhere

up or down usually because youve had a

large safety factor youre going to have

to escalate

that is almost as scary

as picking the first dose why is that

because if you escalate too quickly and

you have a steep slope a narrow

therapeutic index

you can go from a dose thats

pretty well tolerated to one thats

lifethreatening

pretty scary i mean underneath

everything we

first do no harm but its a tough

balance between doing no harm and being

timid

whats the downside of being timid

well if youre an investigator if youre

a patient

the downside is youll get homeopathic

doses

youll get doses that have no chance

of improving your treatment at all

so

in order to maximize the potential

benefit to patients you have to think of

ways of

doing escalations that we never

considered before like escalating within

the same patient

by taking larger steps

um

if youre an investigator

at the time that i first came into this

field thered just been a series of

first and human studies at large cancer

centers that took three years to

complete

so from the time the first dose was

safely given

until the time that the final dose

which is just the beginning of the

process of figuring out whether theres

any activity was defined

that creates a terrible discontinuity

between among the clinical studies

clinical fellows who are designing this

study the clinical fellows who are

running the study and the clinical

fellows who are interpreting it and

trying to write it up afterwards

so its

efficiency is not just a fancy word

efficiency is very important for

patients to get

potentially exciting therapy for

investigators to

to move along with their career and to

keep the whole thing going the conflict

is between

caution

safety efficiency and efficacy no matter

what design you choose to use

youre still going to have to face that

that factor

for um

0 years there was something called the

modified fibonacci escalation scheme

what that meant was that when you

submitted a protocol to your irb or

ethics committee

the escalation procedure was predefined

and that you would follow this

mathematical algorithm for for

increasing the doses

so your safety effect if you look at the

low end of the scale 0 if you have a

0 safety factor

then your starting dose is 0

and if thats safe

where do you go next well in general in

balancing

safety versus a desire to get some

efficacy

you assume i had such a big safety

factor i want something big for my first

step so you double it

all right

and everything is still okay thats the

usual outcome

but youre nervous about continuing the

doubling because

you dont know what you dont know you

dont know where you are in humans

nobody else has been there before

and so this idea that you would

serially reduce the incremental step in

terms of percent escalation

very roughly tied to the fibonacci

series in mathematics became the gold

standard for how

first in human studies were done

again

many inefficient studies because you

reach you cone down to such a small step

that youre

youre youre working hard against inter

subject variability

if you have a dose escalation step of 0

percent

and intersubject variability of 0

you have to be careful about the noise

so a number of adaptive uh designs have

been proposed

not just by myself and my colleagues bob

dedrick bruce chavner at al

but by others in which they try to think

of ways of

finetuning the escalation

scheme so that its no longer predefined

so you tell the irb what your starting

dose is and you tell them how you will

make your adjustments but you dont lock

it down in concrete

so lets talk about what those

principles might be

well

this is a pkpd course

so our fundamental thought

is that concentration circulating in the

body

tells you at least a lot not everything

but tells you a lot about whats likely

to happen in terms of toxicity and

efficacy

indeed

the concentration of drug circulating in

the body

is considered a biomarker

or an end point in many clinical studies

we expect in the toxicity domain

equal toxicity for equal exposure first

in human

is all about hoping you have a

terrifically effective drug

but

the first principle is is it safe

can this structure be given safely to

human beings

so how might you do an adaptive design

well pay attention to what you already

know so if you um give the biggest dose

you think you can to humans you compare

it to to start with you compare it to

how large are those animals tolerated

all right so thats just on the basis of

those and you know thats one way to

escalate but when you consider

interspecies differences in metabolism

youre probably much more interested in

blood levels or concentrations in plasma

because thats what pharmacodynamic

effects are are built upon so you can

change your escalation strategy to a

from a predefined set of numbers

on a universal scale to strategy that

says the size of my escalation steps

will be determined by whether it appears

that were very far away from the target

or were very close and we need to be

cautious

well you dont just say thats a good

idea lets go out and do it you have to

generate a database you have to evaluate

it

retrospectively before you can jump in

so

my colleagues and i did a study of

[Music]

anticancer drugs in in

humans in our program at nci versus

the toxicity and pharmacokinetics that

were done in mouse which are primary

efficacy and sort of an early toxicity

ratio

and the histogram on the left

shows that theres a lot of variability

what have we done were just looking at

the ratio

of dose that causes toxicity

in a human to a mouse

and the good news is the biggest bar in

that bar chart is clustered around one

that says that dose is not a terrible

predictor of toxicity

the dose thats tolerated in rodents may

actually predict

the dose that will ultimately be

tolerated in humans however its far

less than half of the time so we still

need something else

so when we looked instead again this is

retrospectively because you dont do a

study like this prospectively

without a serious database we looked at

those same set of drugs in which we

looked at the area under the curve or

the total exposure

in humans compared to mice

and what did we find

we found that that curve clustered

around one swallowed up some of the two

tails of the curve

so area under the curve did a better job

at predicting toxicity relative toxicity

across species

than just looking at those ratios

the lefthand side of that histogram

um tells you the danger zone

where for some reason humans are

hypersensitive

relative to the nonhuman species that

it was tested in and so at a

at the same relative concentration

humans will have more toxicity you cant

completely eliminate that you just have

to narrow down the number of cases that

occurs

on the other hand to the right of the

tail

are the cases of where humans

can tolerate the maximum concentrations

in rodents without any trouble at all

and you can escalate

four or more times fold

that is a serious efficiency problem

its less of a safety problem

but

its the real world

so thats one one type of design its a

hypothesis that we could improve the way

first and human studies are done by

taking advantage of wellestablished

clinical pharmacology principle

that its the concentration that counts

the dose is just a way of getting the

delivering the concentration to the

individual individual preclinical

species are clinical

for those cases where there are

discrepancies and and so were sort of

satisfied with the results there but but

were curious too and we want to know

why theres a big difference

so earlier in this course sandy markey

taught a couple of courses on how to

measure drugs and how to interpret

structures and

one of the things that he didnt spend

as much time on was species differences

in drug metabolism he told you the tools

of how to develop that

but

earlier in his career he spent a

substantial time

investigating differences

in you know just take halflife as a

parameter so phenylbutazone a drug

thats no longer in the market

for humans anyway

has a threehour halflife in rabbits

six hours across a wide range of species

rat the dog

and then in humans and this is part of

the reason why its no longer in the

market for human has a threeday

halflife in humans

so the experience that you gain looking

at a rabbit a rat guinea pig or a dog

dont adequately prepare you for this

this large difference thats seen in in

humans

we know a lot pharmacogenetics tells us

a lot about the enzymes that

do the metabolism about species

differences

species variation in those we can do

better in predicting it but its always

lurking in in the background so in my

mind

metabolism is the principal compounding

factor confounding factor in first in

human studies

pachytaxal is a very successful

anticancer drug

at the time that it was being developed

all of these principles about

interspecies differences in metabolism

this would be the early 90s now were

just beginning to

sink in and have an impact on the drug

development process

and it was a little bit embarrassing

that we were about to put paclitaxol

into

patients without knowing this are there

any major

landmines in terms of its drug

metabolism

so

the folks in my lab

compared

microsomal metabolism of

in human and rat

microsomes and looked at what happened

fascinating

the

humans make a very unique

metabolite which the arrow at the top

identifies this as the h for six alpha

hydroxypachotaxol

rats make none of it and rats were the

primary toxicology species for this

rats make the biggest thing they make is

pka followed by peak b and humans make

it not at all

what does that mean we dont throw out

everything but it makes you think a

little bit more carefully about how to

interpret your toxicology studies

good news is

a b and h altogether have minor

biological activity for either toxicity

or activity

not so much a problem

they do influence the

amount of parent thats circulating

because the faster its metabolized the

lower its value is but it turns out that

if you just follow the parent

concentration

youll youll be in good shape because

thats where the activity and the

toxicity is

an important lesson important lesson to

learn

frequently cited in the drug drug

interaction area but heres a more

famous one in the drug interactions and

i know youve been very patient in

sitting through a bunch of oncology

examples but lets go to allergic

rhinitis

this is runny nose season right now

and

most of you dont realize that the

original way antihistamines work were by

making you drowsy and you didnt notice

your symptoms

all right that doesnt do anything for

your productivity so the pharmaceutical

industry developed what they wanted to

call nonsedating

antihistamines and my former employer

the fda said why dont we just call it

relatively nonsedating and well all be

happy so thats thats what those

commercials that scroll by on the

television

the most successful the early class was

uh terphenidine which was marketed as

seldane was a prescription drug in the

us it was over the counter

around the world and there was a pending

application at fda for it to become over

the counter

all of a sudden at the emergency room on

the other side of rockville pike in what

used to be called the naval hospital

there were a series of patients who

showed up in their late 0s early 0s

who had bizarre heart rhythms towards

side to point

and they didnt have any history of

heart problems

they

had been taking antihistamines for a

while they were taking terphenidine

and it was just

really confusing to figure out what

happened well what happened is they got

a concomitant infection of some sort and

they started taking

other medications

um

such as ketoconazole or erythromycin

that interfered with the metabolism of

terfenity

and it turns out that when terphenidine

0 milligrams is swallowed

what you see circulating in your body is

no terfinitine at all zero

its all the primary metabolite

fexofenidine which today of course is

marketed as

allegra or the generic form

well who cares about all that stuff well

we do

because theres a

onetoone correspondent relationship

between

the amount the concentration of

terphenidine or effexophenidine that has

the desirable effect

and a 0 000 fold difference

in the toxicity in terms of cardiac ion

channels

remarkable

it was not important as long as every

molecule of terfenidine that was

swallowed got metabolized in the gi

tract in the liver before it circulated

to the heart

but as soon as you

blocked that process with another drug

then you could suddenly measure

targeting circulating in the body and

that could be related to the heart

defect problems so this was the wake up

call

for drug drug interactions thats a

reason we have to read all these

complicated labels

and all these potential drug

interactions that occur because you got

to sort them out you got to prioritize

them

but

you cant overlook them particularly in

patients who

take a half a dozen drugs

all right lets try one more approach

pharmacodynamic approach

so i really like pharmacokinetics helped

my career a lot but its

pharmacodynamics that what were really

interested in

does the drug work

is it good does it have too many side

effects its all pharmacodynamics

and so could we design first in human

trials based on pharmacodynamics instead

of pharmacokinetics

doesnt seem um like theres any reason

not to so you have some kind of

reference dose in the animals typically

a maximum tolerated dose so it might be

just a minimum effective dose

you attach some safety factor between 0

and 0 and thats your starting dose

and then you have a whole rich body of

data from your preclinical studies that

define the target pharmacodynamically

for it if youre trying to inhibit an

enzyme whats the inhibition of the

enzyme

if youre trying to tie up a receptor

and block it what percent blockade do

you need

you have a very rich set of in vitro and

in vivo study in the preclinical domain

why not use that as a reference for

assessing target impact

in humans

and could you make decisions on how

large an escalation

or whether it even stopped the trial
because of futility youre already well
past your target and youre not getting
any benefit humans must be different
there are some studies like this are
done theyre more challenging but i
think the most important thing as i said
at the beginning dont get attached to
any particular design
get attached to the questions that you
want to ask
get attached to what you want to learn
from doing these studies
so as as i was leaving my former
employer to come back here to nci
we were trying to internally where the
fda was a little bit out of the box
trying to
generate more innovative designs in
first in human studies and trying to
enable
academic nonprofit government
investigators to do more limited studies
that would help them
take their laboratorybased studies to
the next step and so we put out a

document called exploratory inds which

essentially permitted

limited human investigation with a more

limited preclinical package

youre exposing fewer subjects youre

doing that in centers that are

incredibly talented in this area and do

intensive monitoring

essentially we were trying to

encourage molecular proof of concept

just what i was saying before

is the enzyme inhibited is the receptor

blocked

and we were also trying to encourage

functional imaging which had been sort

of caught in in a difficult space in the

regulatory world and needed to be well

defined in terms of that can be

a generator of biomarkers and can be

helpful as an exploratory sense as well

at nci

my soontobe colleagues were working on

something called phase zero which was

very much the same thing as lets

up front limit how far were going to go

into the clinic in return for

getting there faster

so as as we saw earlier in this talk the

historical phases of human evaluation

phase one is about safety safety safety

and itd be nice if you could learn

something about activity you should

certainly look

youre likely to find some surprises

phase two is where youre youre really

making your business model

is the activity promising or is it not

can i invest in this compound

or is a five percent response rate too

low

or is it too toxic

and then phase three is comparative is

does this compound does this drug

development program have anything to

offer thats an improvement over current

therapy

phase zero is stepping back from that it

doesnt exist as a

real entity to exist as a concept there

are phase zero studies done ill show

you one of them but its really about

what is the most important thing about

this compound that you want to learn as

soon as possible

everybody would say does it work

well yeah but you got to back off from

that youve spent

millions of dollars figuring out why it

works selecting the thing that has

the best impact on

a particular

mechanistic target

you want to know

whether you actually get the desired

effect you dont get that by just

measuring whatever the dose limiting

toxicity is

or counting the number of responses and

dividing the number of patients that are

on those are incredibly important

endpoints in the trial

but they come later

and to get higher doses require

more safety study preclinically but you

could learn a lot about mechanism of

action you could answer important

questions

if you had a process like an exploratory

ind or a phase zero

i cant tell you

how hard it is to get people to

articulate the question they want the

answer to

i would have thought

everybody can knows what they want

they want to go to the next stage

is essentially what you know i usually

hear what is the key piece of

information some of the sometimes its a

very limited question

that builds on experience with analogs

that had

problem getting in the body or a problem

with toxicity or something like that

but when you really have a novel

chemotype

what is the what it what do you really

want to

do and how are you going to figure that

out

so almost all drugs are given orally

and

they dont work systemically unless they

get absorbed

and

[Music]

they dont always get absorbed

a fair number of drugs are chemically

unstable at ph

in your gi tract

or even unstable if you take proton pump

inhibitors and have ph

theres also a lot of enzymes that line

your gastrointestinal tract

and every molecule essentially

has to go through the liver before it

goes to the systemic circulation

and then theres those formulation

things you swallow a nice

hard pill and it comes out the other end

as a nice hard pill that actually does

happen

so

a key question is

this is my drug this is the thing that i

think has the best chance of working

can i achieve adequate concentration so

thats simple thats not very

complicated

why not do that in your first set of

patients

in a project we did in this building

in on the nci clinical service we were

looking at an enzyme

inhibitor and we wanted to know whether

this dna repair enzyme was inhibited

we couldnt tell that from looking at

bioavailability studies by looking at

whether it was absorbed we could only

look at it

by measuring the products of the enzyme

reaction

all right

did we do it or not

were not interested in whats

circulating in the plasma this is pretty

tough

were interested in what happens

selectively in the tumor and so we have

to look in the tumor pharmacokinetics is

hard enough when you collect

plasma and urine and stool and

occasional opportunistic samples

somewhere else but to design a study

that requires a tumor biopsy it requires

really

good hypothesis and a strong motivated

patient population

and dont do it without an incredibly

welldocumented assay

you know you dont develop your assay

in tumor biopsies you have your abs

assay ready before you get there

so what happened upstairs on the th

floor

so valiparib was a parp inhibitor that

we partnered with abbott pharmaceuticals

on we did the first in human study here

it was a phase zero it was only intended

to be a single dose

a single dose is not going to be

therapeutically effective because you

need to inhibit the dna repair for some

period of time

its unlikely to be toxic as well so the

fda was fine with us choosing this

mechanism of action to go

so we started at single doses of 0

milligrams went up to 0 milligrams

and by 0 milligrams we had reached the

target what was the target

other than wanting to make sure that it

got in the body at all

we looked at the concentrations that

were circulating

in the preclinical studies

that

of tumorbearing animals in which there

was a target effect

so essentially we were saying as youve

learned in many lectures in this course

that the concentration circulating in

plasma can give you some information

about what target youre looking for

this is not the final answer but if you

cant do that then

the rest of the rest of the

process is going to be more challenging

so we met the first goal what about the

second goal and thats

can we get definitive results out of the

tumor tumor sample

and so heres a series of a half dozen

patients that were were studied again

here in this

in this building um in the first in the

phase zero study

and for five out of six

at that dose that achieved adequate

concentrations based on preclinical

studies for five out of six

pretty

much depleted entirely the product of

the enzyme

so we had a dose that

looked good based on preclinical studies

and based on actual studies in tumors

looks like it intended its goal

we had one

tumor that barely responded

that just shows we didnt make up the

data because thats the way real real

data actually works

are we finished

should we invest a billion dollars in

this drug not now theres still a lot to

be done

it could be that theres a disconnect

between the mechanism of action and the

actual clinical antitumor activity a

lot of work to go but youre willing to

make larger investments when you have

these kinds of data

so

we did a variety of studies by looking

at different doses and different time

intervals between

the dosing to help us define

how to do what essentially was

almost going directly to phase two

because we were we were ready weve had

proof of concept we were ready to see uh

see what could be done

we needed to know a little bit about

those ranging and um

dose intervals

let me say something about uh functional

imaging which was the other part of this

guidance um bobbiness gave a talk he was

like the third one in the in the series

uh in the fall

and he covered this from the standpoint

of pet as a tool more to learn something

in particular about the brain

and

um

very very attractive

tool were greatly embedded to the

neuroscientists for here at nih and

elsewhere for developing it but in terms

of new agent development

lets think about the questions again

i want to know if the treatment impacts

the desired target if it doesnt block

the receptor im not going anywhere else

okay so

somebody appointed me the manager of a

billion dollar company to

figure out what things to go im not

going to go further if it doesnt impact

the target its too early

and everything i invest after thats

going to be very high

i do want to know what the minimum dose

it causes in effect

and i want to know what the maximum dose

beyond which you no longer get any

effect

the shape of the dose response curve

and my marketing department has said

that this pill can only be given once a

day because thats what patients like

but i need to know scientifically

whether once a day is the right dose

interval or not and

its very clumsy to do this in just

empiric studies of toxicity and activity

can be done has been done is done

but maybe if we had biomarker driven

[Music]

answers to these questions and maybe if

we use the pet technology we could find

some ways of doing this

with just a handful of subjects

so this is a different version of the

slide that bob inna showed in his talk

back in the fall

which im going to use to address these

three questions so the first question is

so that i can tell that nasty manager

whos analyzing

managing the pipeline

this is an enzyme

monoamine oxidase type b

its a

reversible inhibitor losabamide

investigational

did it do anything to monoamine oxidase

type b and you dont have to go to

medical school or nuclear medicine

school to say

that at  milligrams

twice a day in the upper right hand

corner there is far more bright spots

than there were at the baseline scan in

the upper left corner

furthermore so yes the answer the first

question is yes

the second question the most minimum

maximum doses are whats the shape of

the dose response curve and thats the

lower lefthand current when i double

the dose

the few remaining flickers of candles

that are left in the brain

disappear

ive got complete inhibition im wasting

my time going any higher assuming this

is the mechanism

the third one is the challenge is can i

give this drug once a day or is it going

to take more often it was given twice a

day in the um

[Music]

in the investigational study because the

the established marketed agent depornell

is

is given twice a day so they thought

they would use that schedule

the pet image was taken  hours later

what does that say that picture is

not quite as bright as in the upper left

but its pretty much there

it looks like  hours would in addition

to being impractical would be terrible

it doesnt tell me whether i need to get

i know that every  hours works because

we gave it the idea and we looked at the

end okay

so somewhere between  works and

hours doesnt

is the answer to whether i can give it

once a day

these day this this design

this experiment didnt answer that

question but if we had had a hour

experiment it would have

um

fascinating approach only takes a

handful of subjects to figure out

whether whether youve achieved your

molecular goal or not does this say

whether loseabamide is going to be a

blockbuster drug or not

no

according to published results

lizebramide was pulled from clinical

development because of hepatotoxicity

all the brain scans in the world folks

arent going to tell you anything about

hepatotoxicity and

you can minimize your risk but

youre always looking

so to sort of get up to the wrapup

portion

[Music]

when i first started giving these talks

many people were concerned that first

and human trials were changing right

before their eyes that there were

different questions that were being

asked

everybody was under great pressure to do

them faster

there are all these laboratorybased

correlative studies whereas previously

phase one studies have been

very simple well now

first in human trials arent necessarily

phase one theyre also phase zero

and i think that the community who does

these studies is now comfortable with

that so yes

theres an identity crisis if you think

that your design will work the same for

every drug that comes off your assembly

line

but

the most important thing is youve been

challenged to figure out what design you

really need for your drugs so maybe its

an identity crisis but its good

the other thing and really the last take

home message is that

that is invariant regardless of what

design you use is

no matter what design you use whats

going to be inherent in first in human

studies if its never been in humans

before

theres a good probability that youre

going to see something different in

humans

that you werent prepared for

in all the nonclinical studies that you

do

sometimes its actually a pleasant

surprise

sometimes its annoyance its a scale

you know one end is pleasant in the

middle is an annoyance

and on the far side is its a deal

breaker

a side effect that wasnt predicted

by animals a

molecular biotransformation that wasnt

anticipated

a parallel pathways that overcome

the intended mechanism of action

this is an excuse not to do the best

design you can

but its a cautionary tale that you

always keep looking

and clinical pharmacologists by nature

are often the first time that first

people who regardless of the discipline

who ask questions like well what

happened to the hearing

what happened to the hearing yeah

theres some related molecules to do

that or

hows the kidney function all those data

are there but my goodness theyre piles

of data

you have to look at it

you have to make sure you find the

surprises when they happen

uh lastly i just thank uh my colleagues

uh here at nih and and my former

colleagues at fda for um

helping me learn a lot of this stuff

participate in clinical trials and

the yellow folks around

the edges of this diagram reflects some

of the sites of people whove

signed up and taken for this lecture

they also are representative of the

people that ive collaborated with

outside of the nih at the f and the fda

and i thank all of them for helping me

pursue this interest