we are honored to have dr william

dr figg received his bs in biology from

georgetown college his bsn pharmacy from

stanford university and his doctoral

degree from auburn university he

completed his internship at the

university of alabama at birmingham

hospital and his fellowship in drug

development at the university of north

carolina chapel hill

he also received an mba degree from a

combined program at columbia university

and the london business school

dr figg joined the national cancer

institute in 99

the following year he became head of the

molecular pharmacology section and the

clinical pharmacology program since then

his research has focused on using

pharmacologic principles to optimize the

treatment of cancer and on identifying

genes involved in the development of

prostate cancer

he has been the pi of over clinical

trials for men with prostate cancer

dr figg has over 0 peerreviewed

publications he has received numerous

awards and honors including the leon

goldberg award from ascpt

the allen j brands award from the us

public health service the russell r

miller award from accp

the andrew cargi award from asmus and

the sustained contribution to the

scientific literature award from ashp

dr figg is adjunct faculty at columbias

universitys college of physicians and

surgeons and serves as adjunct at

several schools of pharmacy throughout

the country please enjoy his lecture

my name is william douglas figg i run

the molecular pharmacology section in

the clinical pharmacology program in the

national cancer institute todays

lecture is the introduction to

pharmacology drug development and

clinical pharmacology

the definition of pharmacology is the

branch of biology concerned with the

study of drug actions where a drug can

be broadly defined as manmade natural

or endogenous molecule that exerts a

biological effect on some type of tissue

or cell

clinical pharmacology is the application

of that

it is the science of drugs and their

clinical use

and focuses on the principles of using

pharmacology to treat diseases

theres a tremendous need for clinical

pharmacologists if you look at the

number of drugs that are prescriptions

that americans take each year about 0

percent of americans take at least one

prescription drug about a quarter of the

population takes three or more

prescription drugs

percent take five or more

prescription drugs

and percent of visits to the

physician involves some type of

prescription

four billion prescriptions are filled in

retail pharmacies each year

and the global market for pharmaceutics

is huge

billion dollars

is it was in 0 and approximately half

of those cells are in the us

pharmaceutical products

sell more than billion per year

so lets talk about drug development

its expensive

some estimate 0 million dollars to

bring one drug to market others estimate

that is much higher at two billion

dollars to get a drug to market

clinical development accounts for

percent of that cost

its also time consuming the median time

from synthesis to fda approval for an

anticancer drug is years

in preclinical development 0 years

in clinical development and in fda

evaluation

for other therapeutic classes this is

lower

quicker

years for cardiovascular for example

so this is the way i think about drug

development all the way from the

beginning to fda

so first we have to identify a molecular

target okay now this is a little this is

concentrated towards anticancer

development but in general applies

across all therapeutics classes so

identify a molecular target

design a compound

through computational approaches

or conduct a high throughput screen to

find something that modulates that

target

test the lead compounds in primary and

secondary in vitro assays

synthesize lead compounds

evaluate compounds to determine

molecular pharmacology we have to

understand how its working in the cell

for cancer its important then to submit

it to the nci 0 screening and get those

results and use the compare analysis to

understand the molecular pharmacology

and what cell lines its having activity

in

next its important to develop analogs

structures that are similar so that you

then can compare a structure activity

relationship analysis

lead optimization is the next thing

through medicinal chemistry

additional in vitro experiments may be

needed at this point

determine an acceptable animal

formulation

determine preliminary animal toxicology

i think its important at this point to

figure out if its toxic in animals

assessed by availability and define a

maximum tolerated dose in animals

conduct in vitro experiments in

xenografts okay tumor cell lines

develop a bioanalytical method for

quantitating the drug

usually lcms these days for small

molecules or elizas for biologicals

characterize the preclinical

pharmacokinetics

and this has determined the halflife

the auc how the drug is metabolized

renally eliminated those types of things

determine if the compound is metabolized

is very important as then you can assess

whether there could be pharmacogenetic

concerns

determine plasma protein bonding

as well as renal elimination

develop and validate a pharmacodynamic

assay biomarker assay for

predicting activity

conduct formal toxicology studies for

the fda

gnp production at this point and develop

a human formulation

then file a ind

then its phase one to define the

maximum tolerated dose

characterize the clinical pharmacology

phase two

uh to determine activity uh in a

specific patient population and then

phase three to compare it to standard of

care to see if theres enhanced activity

at this point youre ready to submit to

the

nda to the fda

cancer drugs have the lowest overall

rate of success with just

percent of the drugs that interphase one

ultimately reaching the fda for approval

the highest success rate is at

percent for hematological related drugs

excluding cancer drugs which make up

of the drug programs that are in

development

the overall success rate increases to

9 percent

phase trials are where most drugs fail

only percent of drugs that interface

to go on to phase

either due to failure

of the study of the efficacy or toxicity

or lack of

funding percent of drugs that are

submitted to the fda receive fda

approval

drugs for rare diseases are far more

likely to succeed with percent of

rare disease drugs that enter clinical

trials get fda approval

of drugs that begin phase trials

are later submitted to the fda for

approval

so lets talk about each phase and the

importance of it

phase one

for cancer it is to determine the

maximum tolerated dose for other

therapeutics category its to determine

a recommended phase two dose

characterize the side effects and dlt

understand the pharmacokinetics and

pharmacodynamics

and one question thats still out there

is what is the starting dose for the

phase one for cancer or cytotoxics it is

0 the ld0 for other therapeutic

classes it can be

it is different

for most therapeutic classes

cardiovascular infectious disease etc

phase one studies are done in normal

volunteers okay that is not the case for

oncology phase one trials are done

routinely in patients with cancer and

routinely for those that have failed all

other

standards of care for their type of

tumor

phase two trials determine the efficacy

in different tumor types or individual

populations

refine the pharmacokinetic data

phase twos are typically single arm

typically single institution

and youre trying to maximize the chance

of detecting a clinical response or

biological activity

we typically use a simon twostep

approach

looking for one in to patients if

we see that have activity if we see that

activity in the first to patients

expanded to 0 to 0 patients

if we dont see activity in the first

patients

theres only a 0 percent chance of

rejecting a drug that has a true

response rate of 0 percent okay so the

chance of rejecting something that is

active is pretty low

now theres no standard formula for

making phase three go no go decisions

you have to put together all the data

and realize the next step is going to be

very expensive to do and time consuming

so phase three hundreds of patients

randomized

multiinstitutional and today typically

multiuh

national

response intensive

con control group is usually receiving

standard of care plus placebo compared

to standard of care

plus the investigational drug versus the

investigational drug okay

broad selection of patients to represent

the community

again for oncology the endpoints are

slightly different

the endpoints for oncology time to

progression or progressionfree survival

but the real standard here is overall

survival can we prolong survival

relief of symptoms

and a delay in event

orphan drug status

drugs intended to treat diseases

affecting fewer than 00 000 people

or if its more than two hundred

thousand people because of concerns that

the cells wont be able to recoup the

development cost okay but its usually a

design for a small population gets

orphan drug status from the fda which

allows longer periods of market

exclusivity

types of approval from the fda

theres regular approval and accelerated

approval regular approval direct

evidence of clinical benefit

or improvement in an established

surrogate marker

accelerated approval

surrogate endpoint

likely to predict clinical benefit

and with that

you have to follow up with a phase four

trial

accelerated approval intended to make

drugs available quickly for individuals

or diseases that are very

lifethreatening

approval based on preliminary evidence

such as surrogate marker changes

prior to formal demonstration of patient

benefit

as i mentioned earlier phase four trials

post marketing so you could have

received fda approval

but pharma uses it also to expand market

indications and its required for drugs

that receive accelerated approval the

median duration of conducting a phase

trial is months

lets discuss translating clinical trial

results into the clinic

tannic published a paper which i think

is excellent that compared the overall

survival of dositaxal plus prednisone

for their routine patients they that

they were seeing in their hospital

compared to those individuals that were

enrolled on a clinical trial

patients at their institution

received dosi taxal prednisone for the

treatment of prostate cancer

patients at their institution were

enrolled on a clinical trial

within that population the overall

results were months for the routine

patients

the standard ones that came to the

clinic

versus 0 months for those individuals

that ultimately enrolled on the clinical

trial so you can see the difference that

the published clinical trial results

probably dont reflect what youre going

to actually

achieve within the clinic routinely

tax which is the the paper that

appeared the clinical trial that

appeared in new england journal had an

overall survival of 9 months

if they limited the routine patients

to eligible criteria it did increase it

to months but still never achieved

what appeared in the

the publication

clinical approval success rate for all

anticancer agents is months small

molecules large molecules

agents developed for hematological

malignancies

had a higher clinical uh

approval success rate success of second

or third indication depended upon the

first indication

if the drug did not receive approval for

the first indication

the chance of receiving second or third

indication is very low percent and

percent for second and third

respectively

four main reasons a drug fail

fails lack of efficacy

side effects the pharmacogenetics and

the pharmacokinetics poor

bioavailability

poor halflife

protein bonding concerns drug

interaction concerns

the

historical three principles of

pharmacology were defined in the th

century

each disease has a specific cause for

which there is a specific remedy each

natural remedy has an identifiable

component

the size of the dose determines the

degree of response

perisilis was a swiss physician and is

classified as the far father of

toxicology

he created the dose makes the poison the

concept that distinguishes pharmacology

from toxicology and is really the basis

of dose response relationships

he also said

all substances are poisons

depending upon the right dose

so the difference between pharmacology

and toxicology pharmacology is the

interaction of chemicals and

macromolecules with the biological

system to yield a therapeutic or

beneficial effect

toxicology is the field of science that

helps us understand the harmful effects

of chemicals

substances situations can

have on people animals or the

environment

in medicine

a side effect

whether therapeutic or adverse is

secondary to the one intended okay

so lets look at viagra for example

viagra was synthesized by pfizer and was

thought to be effective in the treatment

of hypertension and angina

a phase one clinical trial was conducted

with the drug and was determined to have

no effect

no cardiovascular effects

however they noted

marked penile erection ultimately the

drug received fda approval for that

indication

so lets talk about adverse events the

adverse events criteria were really set

by the national cancer institute that

went through and graded all potential

side effects both laboratory

and clinical symptoms

grade one mild adverse event grade two

moderate grade three severe adverse

event grade four life threatening grade

five death

so lets look at a few examples here

um

liver function test

alt

you can see that

in the the printing here it may be a

little small um grade

the upper limit of normal

grade to

times the upper limit of normal grade

to 0 times the upper limit of normal

grade greater than 0 times the upper

limit of normal grade is associated

with death

so lets look at symptomatic clinical uh

use of these grading criteria cystitis

going from grade one

asymptomatic

all the way up to significant bleeding

in the urine okay grade five obviously

death

every drug has a therapeutic window

most therapeutic categories this is very

large

for cytotoxic or or chemotherapies

we tend to push the upper limit of

normal

so there is a lawn a point where we go

above it we increase the risk of

toxicity

theres also a lawn or a point plasma

concentration curves are shown here

where

if we dont get above that we have

minimal chance of having efficacy

and that is called the therapeutic

window that that concentration range

between those two okay

again for oncology we tend to push the

upper because most of the drugs have not

been that effective over the years

so lets look at the drug exposure

effect relationship

a dose or a drug comes into the body

input it has to be absorbed if its oral

intravenous ejection is the other

potential route as well as all the other

ones we could think of

its distributed throughout the body it

starts being metabolized and eliminated

at that point

this is what we characterize as

pharmacokinetics

the other lectures throughout this

course will

delve heavily into each of those

processes

then the drug has an effect it can

either be a beneficial effect biological

effect or toxicity

that is the pharmacodynamic effect

its important to realize genetics play

a role in all of these processes whether

that is at the transporter level or the

metabolism level or at the site of the

tissue or the receptor as to whether the

drug will work or not

lets turn to pharmacodynamics

most drugs work via receptor bonding

okay

drug receptor or drug target is a

cellular macromolecule

complex which the drug interacts with to

elicit a response

drugs commonly alter the rate or

magnitude of the intrinsic cellular

response rather than create a new

response

lets turn to

occupancy theory

the response of a tissue to a drug

exogenous

xenobiotic or a ligand endogenous or

exogenous is a function of the number of

receptors that are occupied

cytoreceptor where a drug bonds is the

bonding site

the concentration of the drug it is an

important factor for the extent of the

receptor bonding and the affinity for

that receptor is important

typically need to reach a threshold of

receptors to get the effect youre after

agonist effect positive effect on the

receptor

drugs that bind to physiological

receptors

and mimic the regulatory effect of the

endogenous ligament

primary agonist is a drug that bonds to

the same recognized site of the receptor

as the endogenous ligand

allosteric agonist is a drug that binds

to a different region of the receptor to

induce its effect

allosteric agonists still mimic the

effect of the primary agonist its just

bonding at a different part of the

receptor the protein

antagonism

drugs that block or reduce the action of

the agonist and there you can have

competitive noncompetitive or

functional competitive competes directly

with the agonist for the same site

and overlaps the receptor

noncompetitive interacts with a

different part of the receptor and

functional indirect inhibitor the

cellular or physiological effects of the

agonist

so lets look at

one example here

the engine receptor the angular receptor

testosterone comes into the cell

by five alpha reductase its converted

to dht what is a five alpha reductase

inhibitor um

enzyme inhibitor

finasteride okay

so dht then bonds to the androgen

receptor which is stabilized by heat

shock proteins and then translocates

into the nucleus to bond to the engine

response element

now

weve we had three known androgen

receptor antagonists flutamod by

kaludamod naludama all of them were not

very specific not a high affinity for

the receptor

more recently a drug enzoludamod has

received approval this is looking at

three kaplanmeier curves from the

postchemotherapy

development program for insalutamod the

trial was called a firm

but just look at the a panel there

overall survival was insaluta mod

versus placebo

post chemotherapy post

the overall survival benefit was

statistically significant towards

insulitamide and again all this drug

does is bond to the energy receptors to

prevent it from translocating into the

nucleus so its a receptor antagonist

now we can have partial agonists as well

they cannot produce the maximum response

of which

of which the tissue is capable

even when it bonds to the same number of

receptors

drug properties

specific bonding of drugs to receptors

depend on the physical and chemical

properties of the drug

important factors include the pka

confirmation and stereochemistry

warfarin for example is a racemic

mixture of snr

enantiomers

s is four times more potent than r

other examples include antiarrhythmic

drugs

and antihypertensive agents

another example is thalidomide

thalidomide everyone remembers the

tragic story

of some 0 000 uh infants being born

with a birth defect in the late 90s

early 90s primarily in europe canada

and australia

from the mother taking as little as one

single dose of thalidomide

the highest risk for the trattogenicity

complications were when the drug was

taken between week and

and it turns out the r

is probably the r enantiomer is probably

what results in the phys

the the the uh pharmacological effects

of thalidomide however the s is probably

what results in the

tradogenicity

receptor properties

contain hydrophobic

often inside protein

or the lipid biolater bio layer

and hydrophilic protein exterior segment

of the protein

bonding site possess unique chemical

properties based upon unique folding of

the pr protein

drug receptor bonds there are really

four types

van der waal

hydrogen ionic and covalent

so lets look at a few examples there

matinib or gleevec interacts with the

bcr able kinase okay

it fills in the space of this

kinase there you can see the van der

waal interactions that occur in the

panel b

and then in panel c you realize that it

prevents phosphorylation uh happening

which results in the inactivation

gleevec was a very special anticancer

drug

that was very very active and was noted

in early phase and phase

trials

one of the first publications appeared

in new england journal for the treatment

of cml

and these are the kaplanmeier curves

and you can see the imatinib versus the

standard of care at that time

it quickly became the standard of care

and has really prolonged survival for

this disease

lets turn to seraphinib

seraphinib is a tki

that has effects on a lot of different

kinases okay now the important thing

here is to look at the ic0

and you can see the range of activity

the potency for each one of these

kinases okay raph one for example six

nanomole uh um

we can go over to vgf at 90 um

fgf for example 0 nanomole so

in certain kinases shrapnel is much more

potent

and this is what we have seen with all

the different tyrosine kinases they have

different activity against each of these

uh growth factors or kinases

with that

theres been

different clinical activity as well

one

seraphinib hepatocellular as well as

renal cell cancer it has received fda

approval

drug receptor interactions

its important to understand affinity

intrinsic activity selectivity

and numbers how many

receptors are available for bonding

affinity how well the drug bonds

intrinsic activity

produce a measurable effect

selective

intended target is it hitting the

intended target

so lets look at the adrenergic receptor

selectivity

agonist versus antagonists you can see

different drugs listed there dopamine

for example phenylephrine on the agonist

side

on the antagonist side you can see a

list of drugs listed there

and depending upon which one theyre

trying to hit the alpha or the beta

receptor alpha alpha beta beta

beta

induce fit binding

binding of a drug to the receptor

results in a confirmation change in the

receptor that enhances the affinity of

the drug for the receptor

this goes beyond the static lock and key

idea of a drug hitting a receptor

change in the shape

induces induced by the drug is often

identical to what happens with the

endogenous ligament

insulin for example is a good is a good

example of this

next lets turn to some of the

chemotherapies and how they actually

work

platinum is is a great example in that

it forms these adducts in the dna

okay

and this prevents replication

this bonding this platinum bonding adder

prevents the dna from

breaking and dividing

next lets turn to examples of drugs

that inhibit transporters okay and a lot

of drugs inhibit this and the need to

understand the ki

the ki is the inhibitory inhib

inhibition disassociation constant

so this is looking at data from my

laboratory

of a drug that was identified through a

high throughput screen at

the university of kansas uracilic acid

as an inhibitor of oatpb

we use three substrates testosterone

dihydrotestosterone

and anderstein dione and characterize

the ki for each of these okay so was

uracilic acid able to block the

transport in of these drugs of these

substrates

rational drug design

the application of structure activity

relationships to develop new drugs with

improved pharmacological uh effects okay

its been around for years i mean the

one of the first was the the

barbiturates okay patented by bear

used for sleeping aid in the 9 early

900s

but its the idea of changing the

structure in order to or or designing

something to actually hit the intended

target

so im going to go back to thalidomide

because i think its a good example that

had a drug that has a lot of different

activity for example its known to

affect t cells ultimately got

fda approval for the treatment of

multiple myeloma

it was initially developed for sleep aid

okay

but its affecting

cytokine productions its affecting

cox tnf in an inflammatory cascade and

it also has effect on cerebellum

with all of these different activities

we ask could we identify drugs that were

more specific for one of the of the the

molecular effects

so we have synthesized a large number

three over 00 analogs and this is just

one example of how we go about trying to

identify one with enhanced

antiangiogenic properties using a

zebrafish model that measures the length

of growth of the blood vessels

putting the drugs the different analogs

in the water were we able to block that

expansion or that

growth of the

endothelial cells

the highest antiangiogenic had the

shortest vascular effect and the fewest

vascular numbers

those with less effect were farther

along on these curve

we did the same thing trying to optimize

the antiinflammatory effects

using gfplabeled neutrophils

and looking at the recruitment to a a

a slice in the zebrafish tail

and then we labeled or or plotted out

all the different analogs as to how they

were able to affect the the recruitment

of those neutrophils towards uh that

injury

ultimately we came up with this type of

chart

trying to of the 0 analogs we

developed on one side what were the most

effective for uh inhibiting angiogenesis

on the right hand side what were the

most effective at having

antiinflammatory activities we narrowed

that down to analogs

that were antiangiogenic 0 that were

antiinflammatory and three that had

effects across both ways

then we took those 9

compounds and have taken them into

models to try to develop the best one

and identify a lead compound

but most importantly with all of those

weve been able to develop a structure

activity relationship so that we can

then

determine

what side chains are necessary for what

activity

and this is the approach that is is

really powerful as you then can predict

and develop new agents

the fda ultimately approved

two analogs of thalidomod

both of them for the treatment of

multiple myeloma linolitamod and

pomalidomide

i hope youve enjoyed todays lecture

clearly weve not discussed all the

mechanisms of action of all the drugs

there are more out there that work

differently i tried to give you an

overview of pharmacology and how it

pertains in the drug development process

nonetheless if you have questions please

contact the course coordinator

thank you for listening