Development of a Medical Animation on Acetaminophen Metabolization and Hepatotoxicity

Julia A. Klein

M.S. Biomedical Visualization
University of Illinois at Chicago

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UIC UNIVERSITY OF ILLINOIS AT CHICAGO

Overview

- Project Inspiration
- Research Questions
- Information Research
- Animation Workflow
  - Roles
  - Production Steps
    - Pre-production
    - Design
    - Production
    - Post-production
  - Project Management
- Conclusions

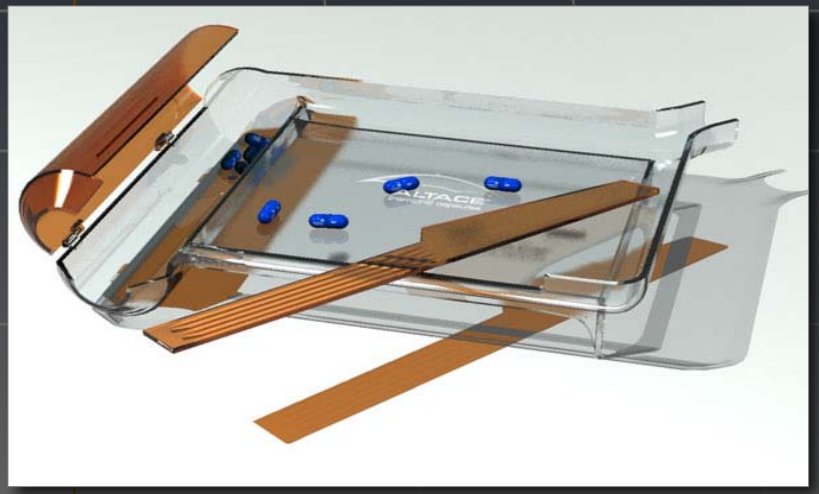
Project Inspiration

Why this topic?

Project Inspiration

Pharmacy

- Pharmacy technician role
  - Fill and deliver prescriptions to patients
- Pharmacist role
  - Patient education
  - Knowledge of APAP danger



Project Inspiration

Medical Media Agency

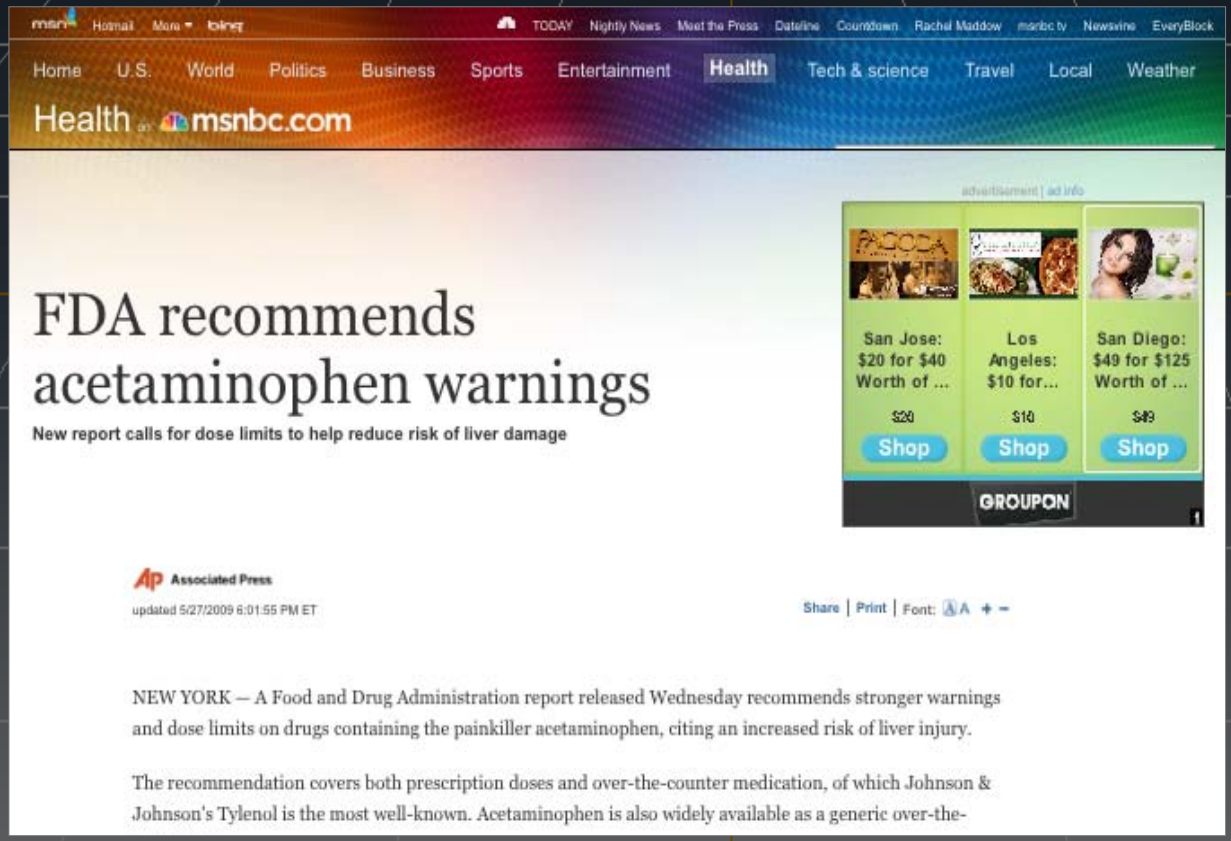
- Visual Science Specialist Role
  - MOA and MOD 3D animations

http://www.eveo.com/

Project Inspiration

Warnings on acetaminophen in the news

- 2009 FDA recommendations



http://www.msnbc.msn.com/id/30969044/

Research Questions

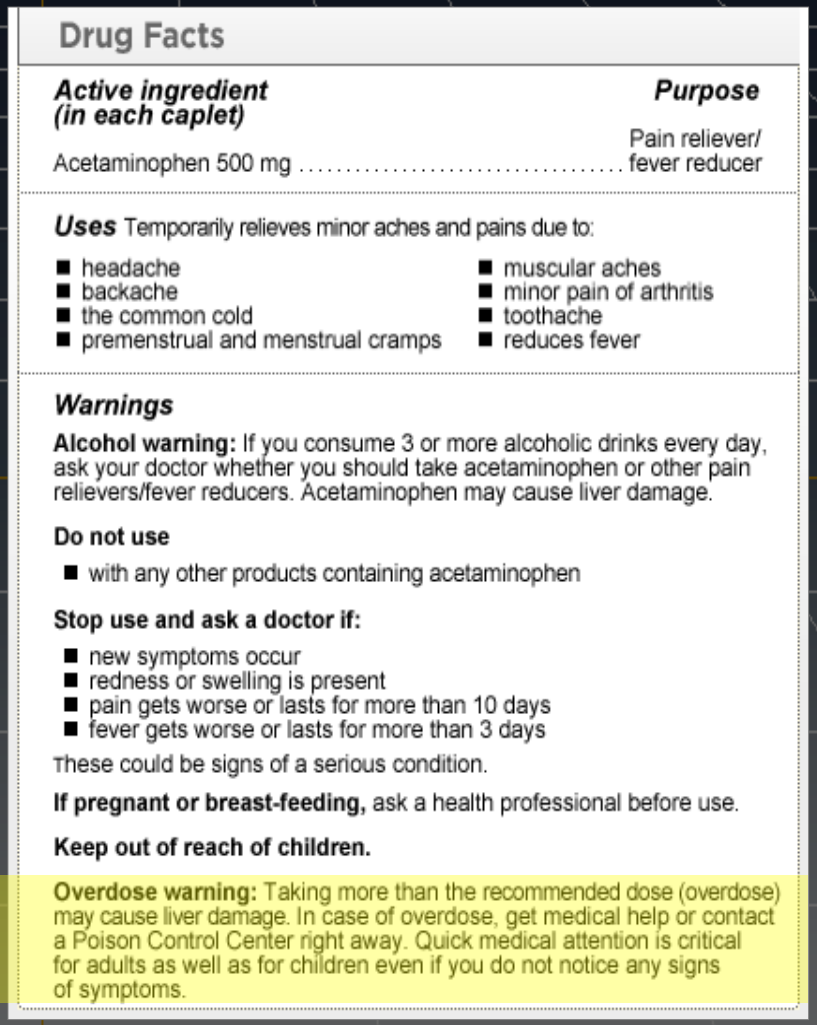
- How can the APAP metabolic pathway and its potential for hepatotoxicity be visually explained to an audience of healthcare providers?
- Could a short medical animation be created that represents the APAP metabolic process?
- Can the production roles and steps from a professional medical animation workflow be consolidated and done by one researcher rather than a team of people?

Information Research

TYLENOL® ACETAMINOPHEN

Tylenol® Drug label

- Active ingredient
- Purpose & Uses
- Warnings
- Overdose warning



Drug Facts

Active ingredient (in each caplet) — ***Purpose***

Acetaminophen 500 mg ..... Pain reliever/ fever reducer

Uses Temporarily relieves minor aches and pains due to:

- headache
- backache
- the common cold
- premenstrual and menstrual cramps
- muscular aches
- minor pain of arthritis
- toothache
- reduces fever

Warnings

Alcohol warning: If you consume 3 or more alcoholic drinks every day, ask your doctor whether you should take acetaminophen or other pain relievers/fever reducers. Acetaminophen may cause liver damage.

Do not use

- with any other products containing acetaminophen

Stop use and ask a doctor if:

- new symptoms occur
- redness or swelling is present
- pain gets worse or lasts for more than 10 days
- fever gets worse or lasts for more than 3 days

These could be signs of a serious condition.

If pregnant or breast-feeding, ask a health professional before use.

Keep out of reach of children.

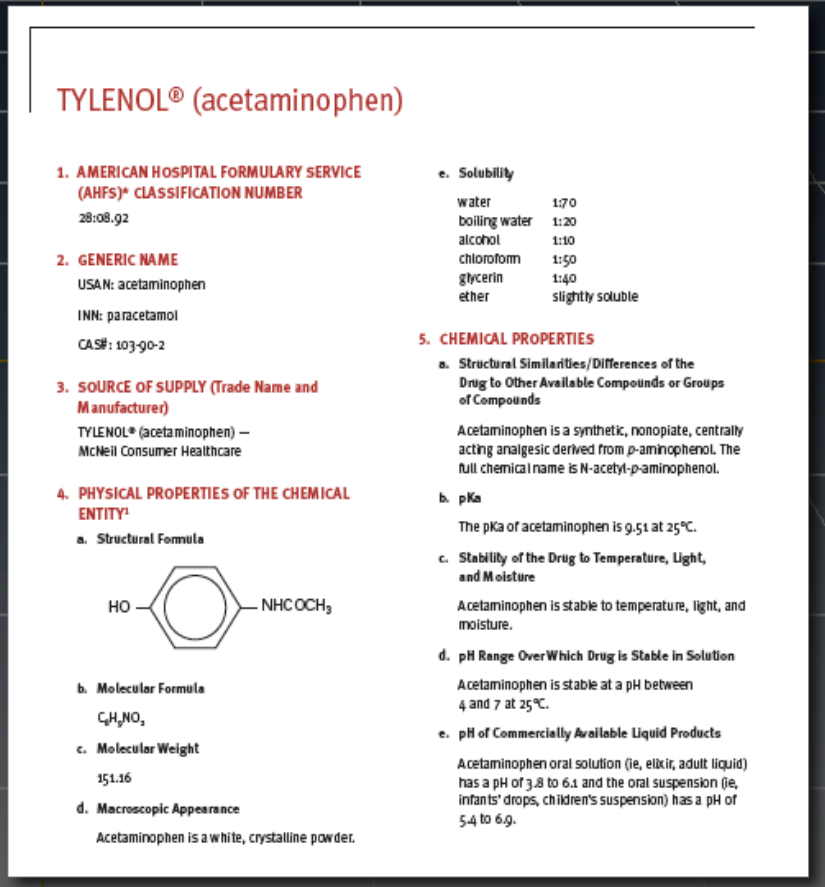
Overdose warning: Taking more than the recommended dose (overdose) may cause liver damage. In case of overdose, get medical help or contact a Poison Control Center right away. Quick medical attention is critical for adults as well as for children even if you do not notice any signs of symptoms.

http://www.tylenol.com/page.jhtml?id=tylenol/painex/subhowto.inc

Information Research

Tylenol® Professional Product Information (PPI)

- Drug facts
- MOA
- MOD of overdose
- Overdose treatments



TYLENOL® (acetaminophen)

1. AMERICAN HOSPITAL FORMULARY SERVICE (AHFS)* CLASSIFICATION NUMBER

28:08.92

2. GENERIC NAME

USAN: acetaminophen

INN: paracetamol

CAS#: 103-90-2

3. SOURCE OF SUPPLY (Trade Name and Manufacturer)

TYLENOL® (acetaminophen) —
McNeil Consumer Healthcare

4. PHYSICAL PROPERTIES OF THE CHEMICAL ENTITY[1]

a. **Structural Formula**

b. **Molecular Formula**

$C_8H_9NO_2$

c. **Molecular Weight**

151.16

d. **Macroscopic Appearance**

Acetaminophen is a white, crystalline powder.

e. **Solubility**

water	1:70
boiling water	1:20
alcohol	1:10
chloroform	1:50
glycerin	1:40
ether	slightly soluble

5. CHEMICAL PROPERTIES

a. **Structural Similarities/Differences of the Drug to Other Available Compounds or Groups of Compounds**

Acetaminophen is a synthetic, nonopiate, centrally acting analgesic derived from *p*-aminophenol. The full chemical name is N-acetyl-*p*-aminophenol.

b. **pKa**

The pKa of acetaminophen is 9.51 at 25°C.

c. **Stability of the Drug to Temperature, Light, and Moisture**

Acetaminophen is stable to temperature, light, and moisture.

d. **pH Range Over Which Drug is Stable in Solution**

Acetaminophen is stable at a pH between 4 and 7 at 25°C.

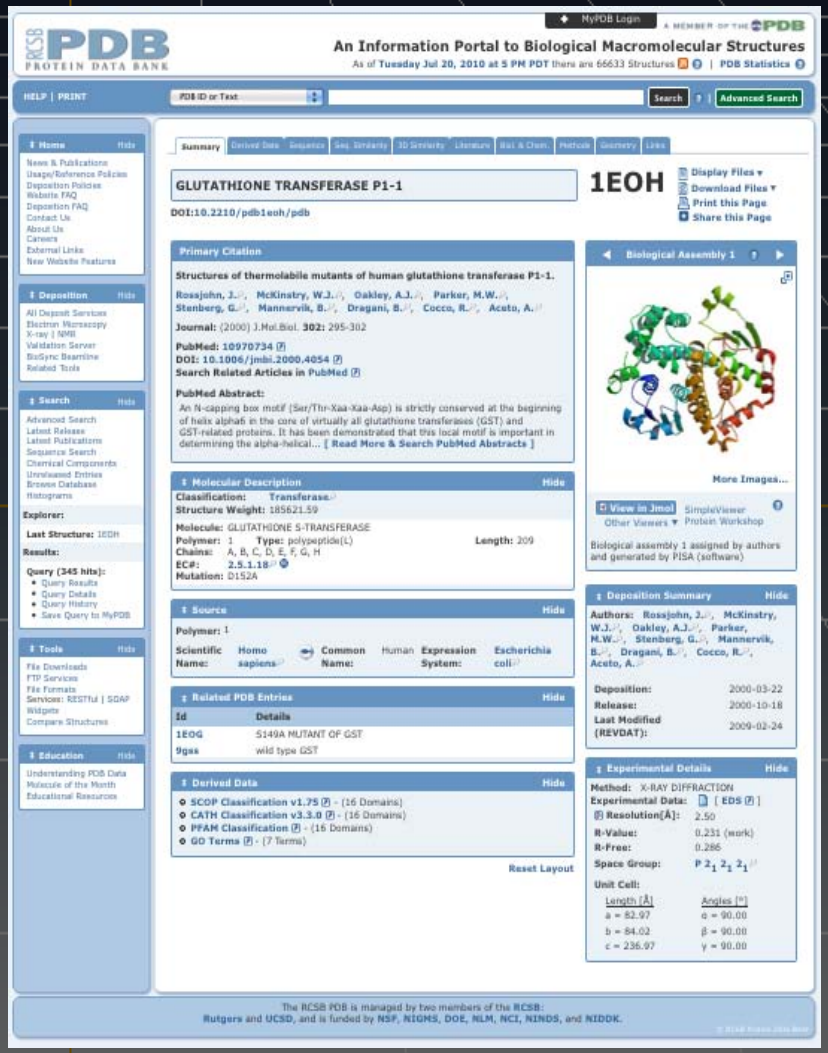
e. **pH of Commercially Available Liquid Products**

Acetaminophen oral solution (ie, elixir, adult liquid) has a pH of 3.8 to 6.1 and the oral suspension (ie, infants' drops, children's suspension) has a pH of 5.4 to 6.9.

Information Research

Protein Data Bank

- Information
- 3D .pdb files

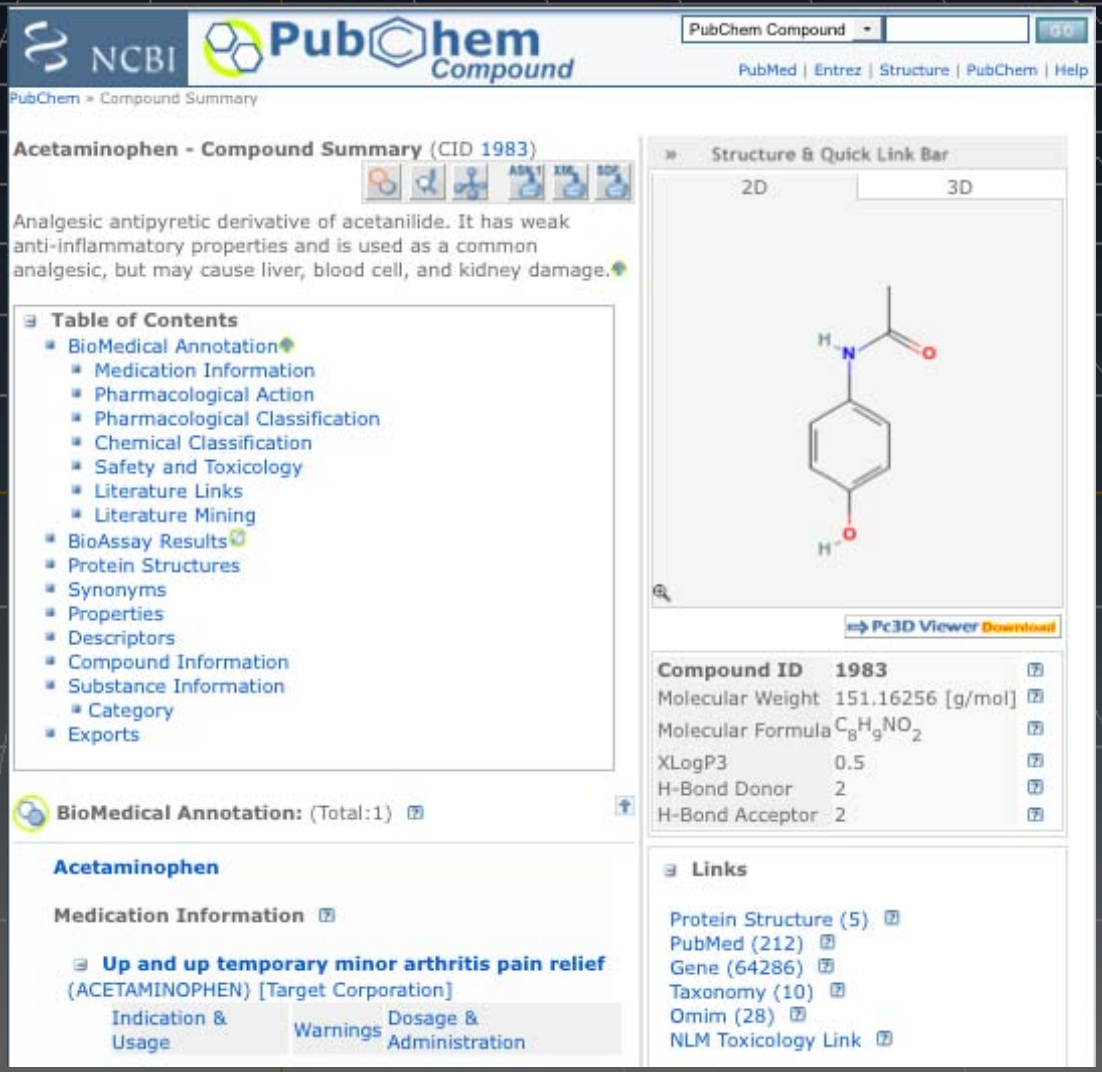


http://www.pdb.org/

Information Research

PubChem

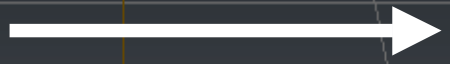
- Information
- 3D .sdf files



http://www.ncbi.nlm.nih.gov/

Animation Workflow

- Based on a professional medical animation workflow
- Roles
  - Science content consultant
  - Medical writer
  - VO talent
  - Producer
  - Art director
  - Storyboard artist
  - 2D artist
  - Modeler
  - Animator
  - Compositor
  - QA
- Adaptation for one researcher



One Researcher?

Animation Production Steps

- Pre-production
- Design
- Production
- Post-production

Pre-Production

- Content development
- Science reference deck
- Script
  - Outline
  - Voice over (VO)
  - Animation notes
- Storyboards
- Animated storyboards

Science Reference Deck

Character Name (molecular level)	PDB/ PubChem	Also known as/ Type	Size/Weight	Pronunciation	Notes
Acetaminophen	CID_1983	APAP, paracetamol, Tylenol®	151.17 g/mol	ə-ˌsē-tə-ˈmi-nə-ˌfən, ˌa-sə-tə-	
Acetaminophen cysteine	CID_83997	APAP metabolite	254.31 g/mol	cys·teine ˈsis-tə-ˌēn	
Acetaminophen glucuronide	CID 83944	APAP metabolite	327.29 g/mol	gluc·uro·nide glü-ˈkyur-ə-ˌnīd	
Acetaminophen sulfate	CID 83939	APAP metabolite	231.23 g/mol	sul·fate ˈsəl-ˌfāt	
Acetaminophen glutathione	CID_83998	APAP metabolite	327.29 g/mol	glu·ta·thi·one ˌglüt-ə-ˈthī-ˌōn	
Acetaminophen mercapturate	CID_539698	APAP metabolite	312.34 g/mol	mer·cap·TUR·ate	
NAC	CID_12035	N-acetylcysteine, overdose antidote	163.19 g/mol	ace·tyl·cys·te·ine ə-ˌsēt-ᵊl-ˈsis-tə-ˌēn	
Cytochrome P450	2J0D	Enzyme, CYP2E1, CYP1A2, CYP3A4	Length [Å] a = 67.25 b = 210.71 c = 161.25	cy·to·chrome ˈsīt-ə-ˌkrōm	
Glutathione	CID_124886	GSH, tripeptide, cofactor	307.32 g/mol	glu·ta·thi·one ˌglüt-ə-ˈthī-ˌōn	
Glutathione transferase	1EOH	Enzyme, protein, polypeptide	Length [Å] a = 82.97 b = 84.02 c = 236.97	glu·ta·thi·one ˌglüt-ə-ˈthī-ˌōn	
NAPQI	CID_39763	N-acetyl-p-benzoquinoneimine, APAP bioactive metabolite	149.15 g/mol		
COX	1PRH, 4COX	Enzyme, Cyclooxygenase	Length [Å] a = 179.80 b = 133.60 c = 118.40		Not used in the animation
Character Name (cellular/systems level)					
Liver	N/A	Organ			
Hepatocyte	N/A	Cell		he·pa·to·cyte hi-ˈpat-ə-ˌsīt	
Smooth endoplasmic reticulum (ER)	N/A	Organelle		en·do·plas·mic ˌen-də-ˈplaz-mik re·tic·u·lum ri-ˈtik-yə-ləm	
Golgi apparatus	N/A	Organelle			

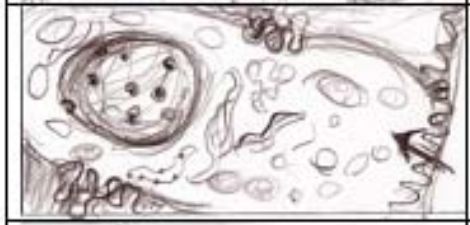
Script Outline

Script outline
UICJAK Acetaminophen Metabolism
3-29-10

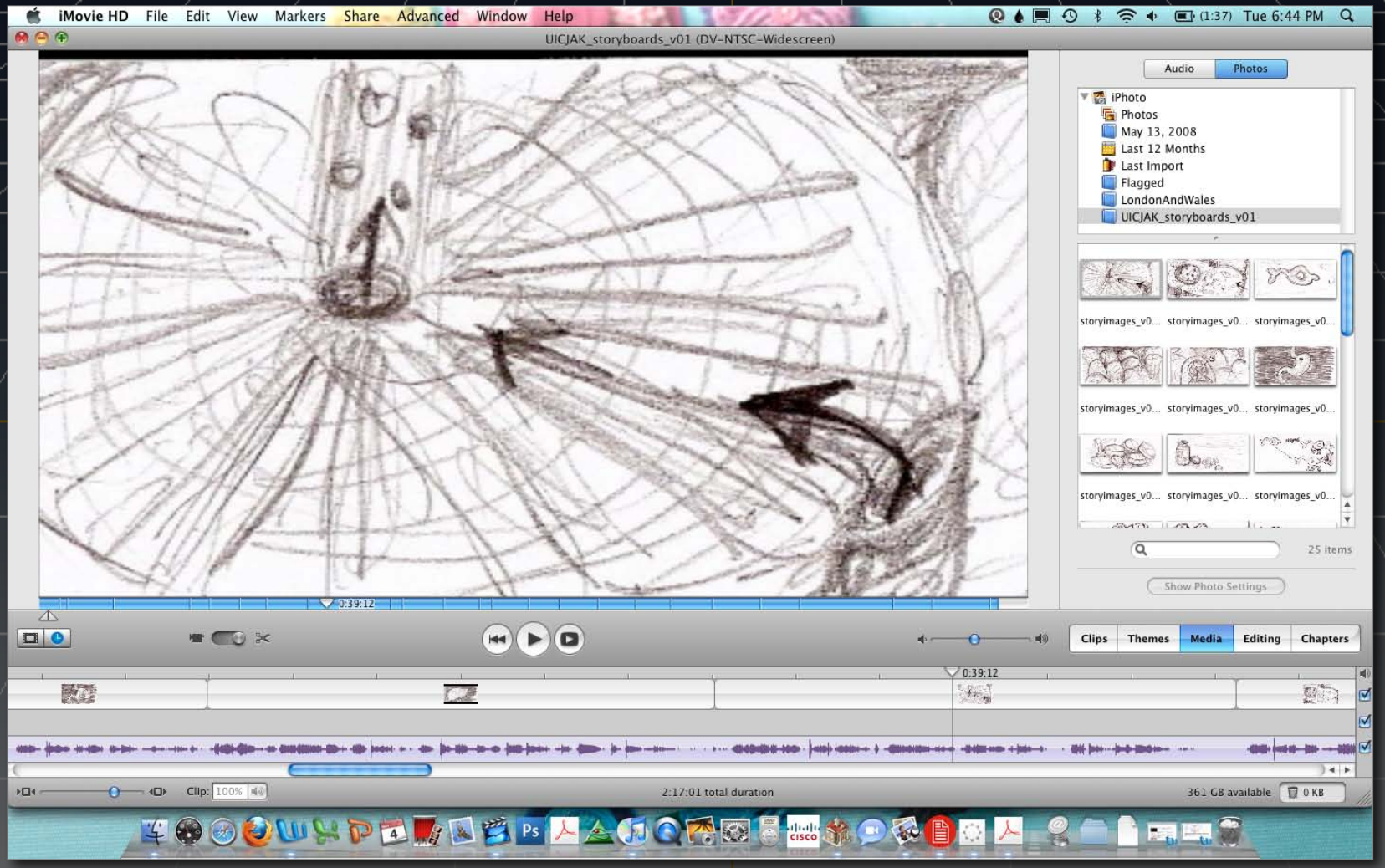
1. Acetaminophen (APAP)
    a. Basic details
        i. Drug type
        ii. Dosage amounts
    b. Absorption
        i. Dissociation of tablet in upper GI (reveal of molecular structure)
        ii. Entry into bloodstream (by capillary)
    c. Function
        i. Analgesic
        ii. Antipyretic
        iii. Inhibition of COX enzyme
2. APAP Metabolism
    a. Site of metabolism
        i. Gross system level - Liver
        ii. Cellular level - Liver cells (Hepatocytes)
        iii. Molecular level - Hepatocyte interior (Smooth ER)
    b. Pathways of metabolism - APAP metabolites in urine {{127 Tylenol 1999; }}
        i. Conjugation with glucuronide to glucuronide 46.8 – 62.2%
        ii. Conjugation with sulfate to sulfate 25.4 – 35.9%
        iii. Oxidation to NAPQI "Oxidation via the cytochrome, P450-dependent, mixed-function oxidative enzyme pathway to NAPQI"
3. APAP hepatotoxicity
    a. NAPQI Deactivation {{127 Tylenol 1999; }}
        i. To mercapturate 2.7 – 5.0%
        ii. To cysteine conjugate 2.1 – 3.0%
        iii. Free acetaminophen in urine 3.4 – 8.7%
    b. Overwhelming of pathways
        i. Too much APAP (overdose)
        ii. Not enough GSH to deactivate NAPQI
    c. Damage…
        i. to intracellular structures
        ii. to hepatocyte
        iii. to liver
    d. Prevention
        i. Antidote
        ii. Prevention of overdose

- Bullet point list
- Names of characters
- Story order

Script and Storyboards

Storyboards	VO	Characters	Notes
	APAP enters the bloodstream and is carried to sites of action.		Picture-in-picture cross fades to show APAP passing though the surface of the villi into a blood vessel and swept away.
	The liver metabolizes APAP and produces metabolites required for function.	Liver	Stomach fades off and liver fades on.
	Many metabolic pathways occur in the liver to rid excess APAP and other substances from the body.	Liver Lobule	Cut to interior of liver. Healthy hepatocytes are arranged in a symmetrical pattern. Blood cells are flowing along arrow path.
	APAP is metabolized in the hepatocyte's smooth endoplasmic reticulum.	Hepatocyte	Cut to single hepatocyte that nearly fills the screen. Simple cellular contents are shown including; nucleus, endoplasmic reticulum, golgi, mitochondria etc.
	The majority of APAP...	APAP	Cut to a simple intracellular space environment, the same color of the smooth endoplasmic reticulum. The APAP molecule structure is shown. More molecules will be seen in the background throughout all molecular shots.

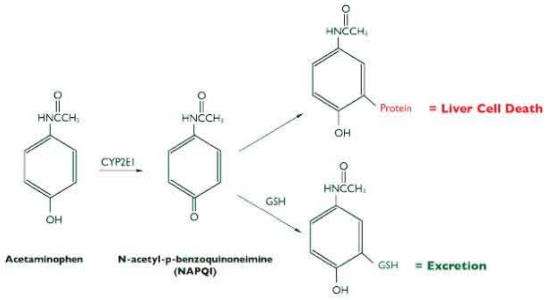
Animated Storyboards - iMovie

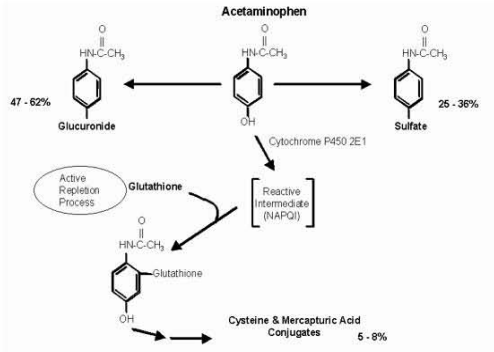


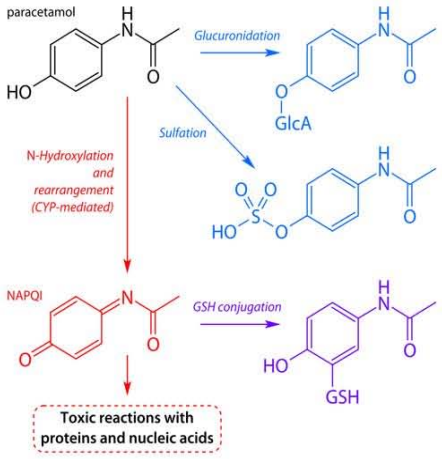
Design

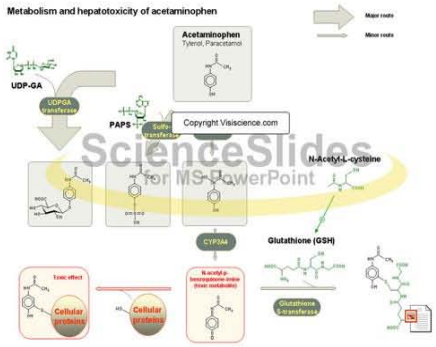
- Mood Boards
- Concept Art
- 3D Models
  - Model Book
  - Modeling
- Textures and Lighting

Mood Board - Metabolic Pathways









APAP Metabolic Pathways

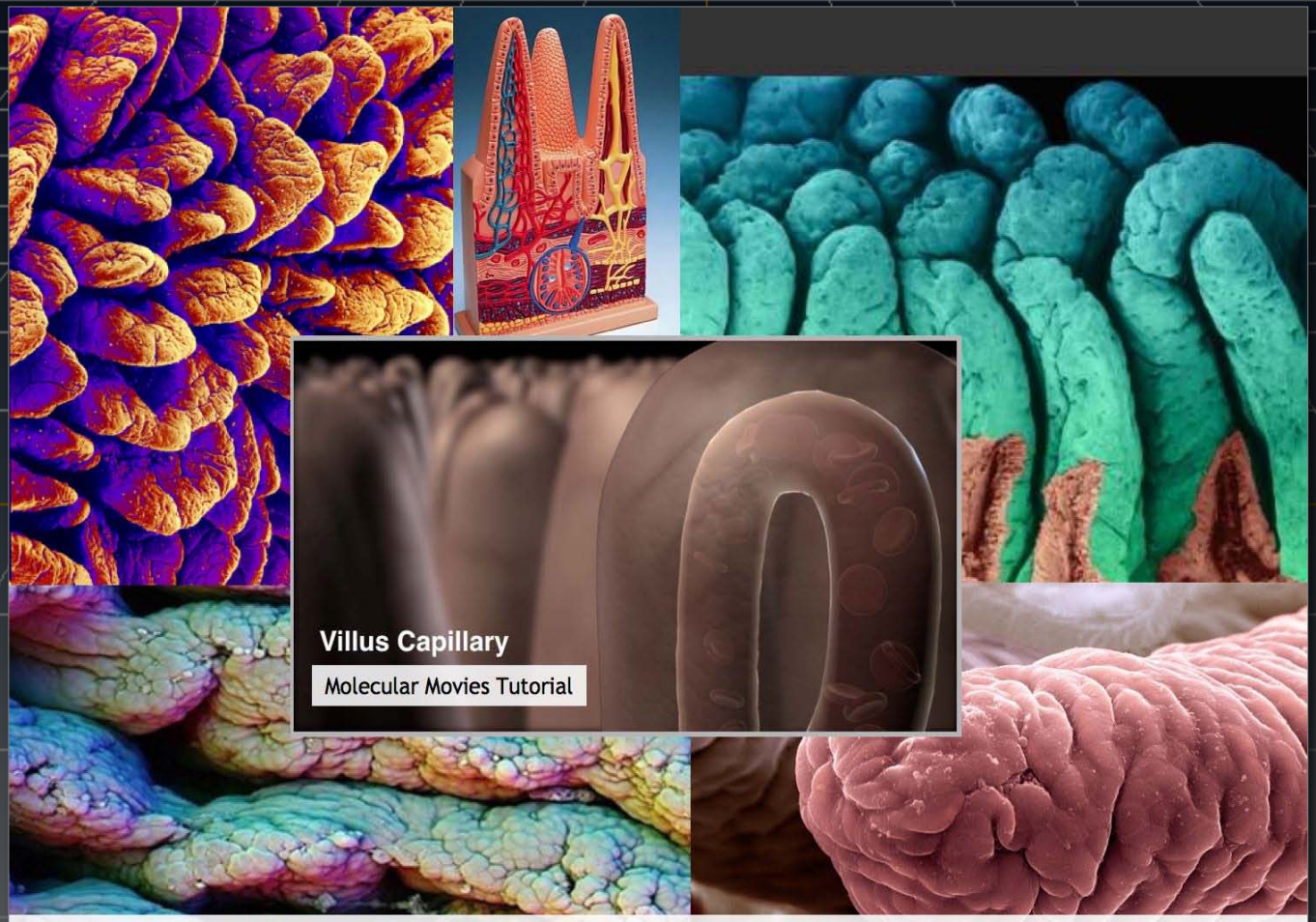
These are some of the various metabolic pathways that will be shown in the animation. The animation will present them much more dynamically as opposed to these static illustrations.

Mood Board - APAP

APAP Tablets

The model of the APAP bottle will resemble a bottle of an over the counter product. The modeled tablets will have a chalky white surface.

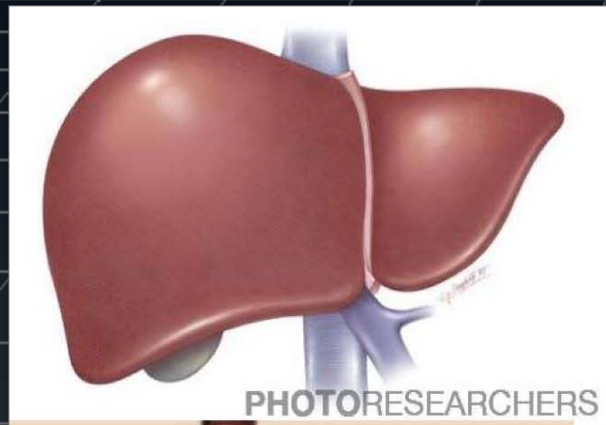
Mood Board - GI Tract Villi

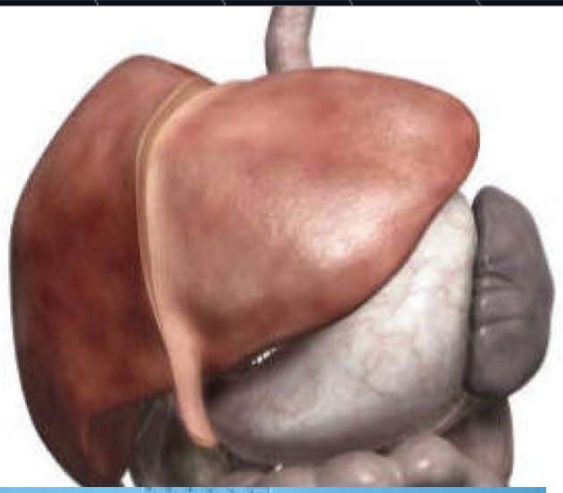


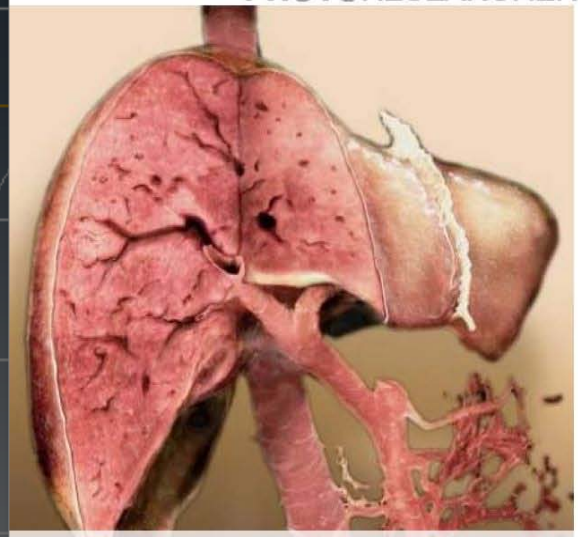
GI Tract Villi

The scene with the stomach will feature an overlay of a villus capillary showing the site of absorption. A tutorial will be referenced from http://www.molecularmovies.com/learning/index.html

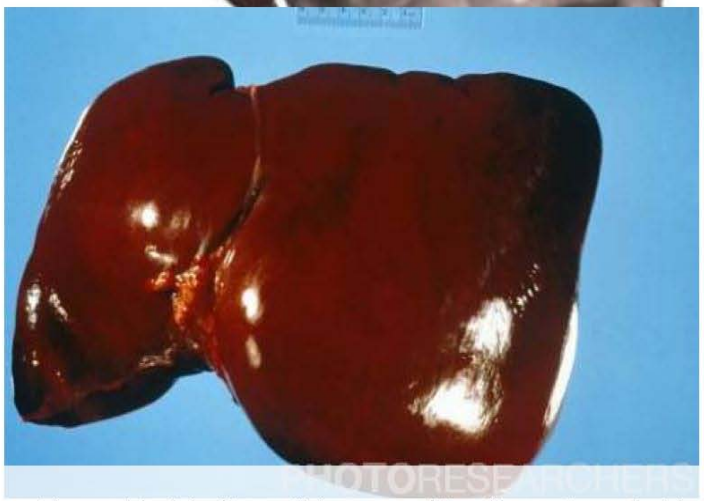
Mood Board - Liver





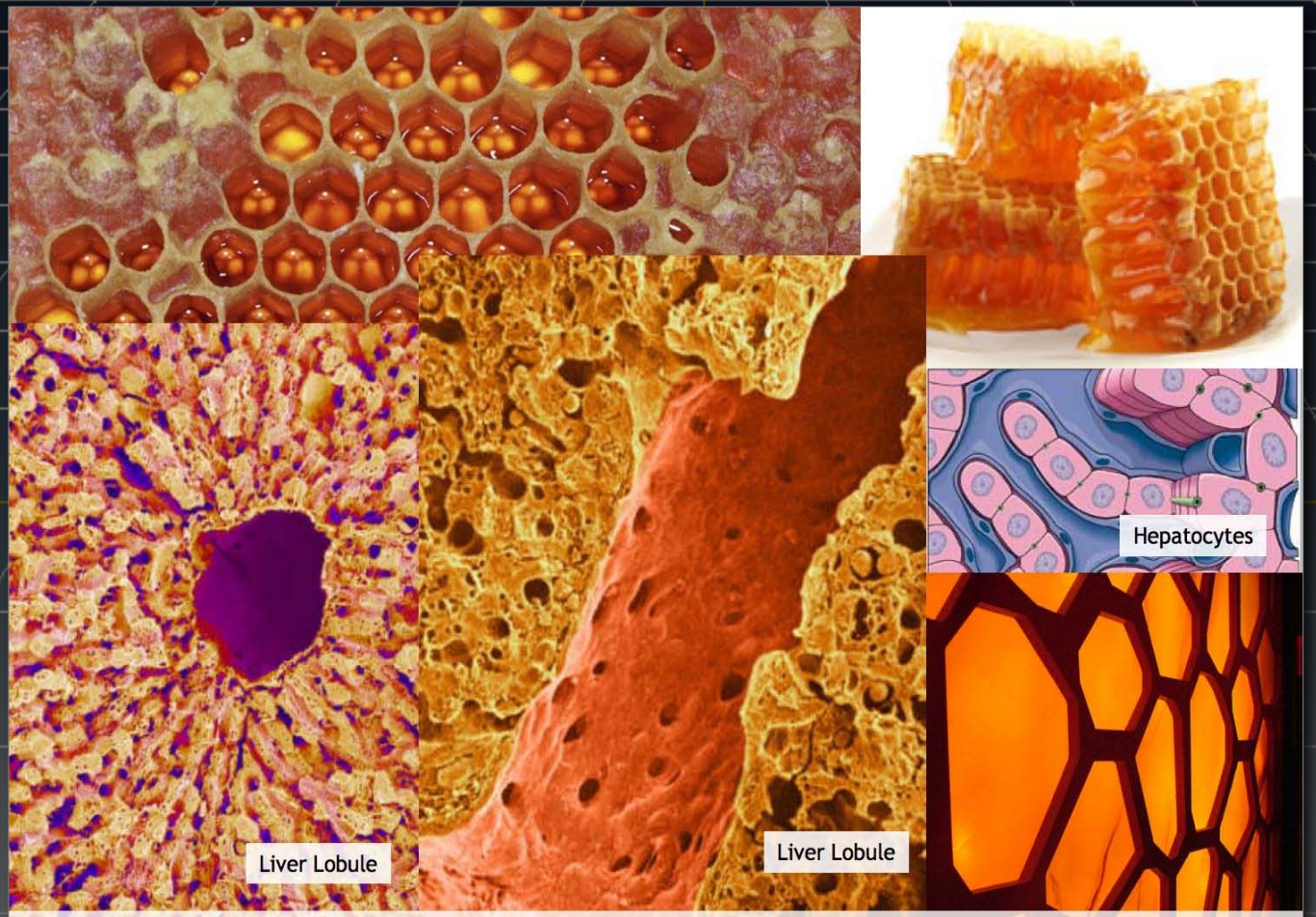


Liver



The model of the liver will be textured in a illustrative style. The stomach (not shown) will also match this style of representation.

Mood Board - Healthy Hepatocytes



Hepatocytes - Healthy Cells

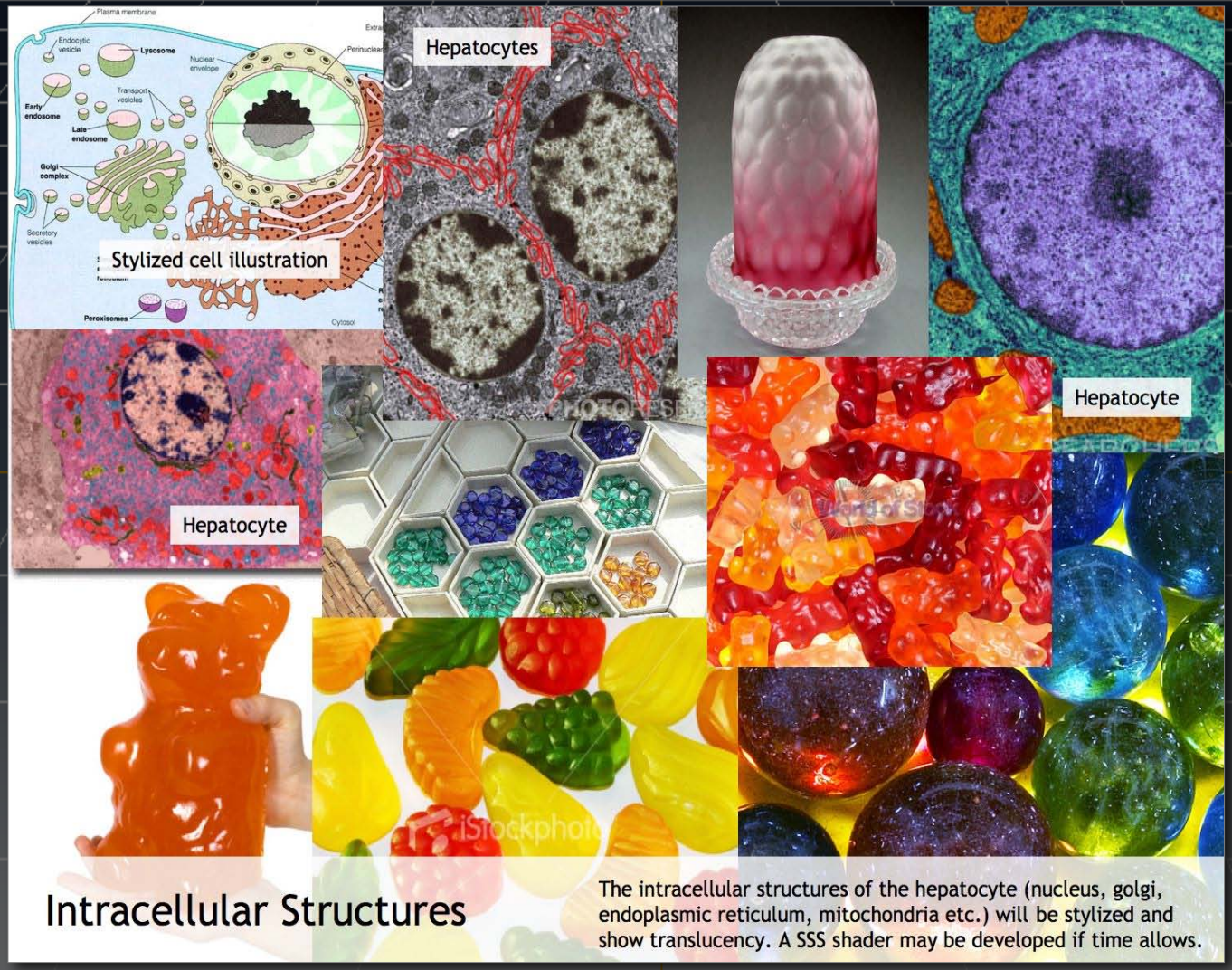
The interior of the liver (liver lobule) will be healthy and brightly colored/lit. Color and surface texture will indicate healthy cells. These bright colors will also be used for the single hepatocyte.

Mood Board - Damaged Hepatocytes

Hepatocytes - Damaged Cells

The interior of the liver (liver lobule) will be damaged and dimly colored/lit. Color and surface texture will indicate damaged cells. These colors will also be used for the damaged hepatocyte.

Mood Board - Intracellular Structures



Mood Board - Metabolites

APAP/Metabolite Molecules

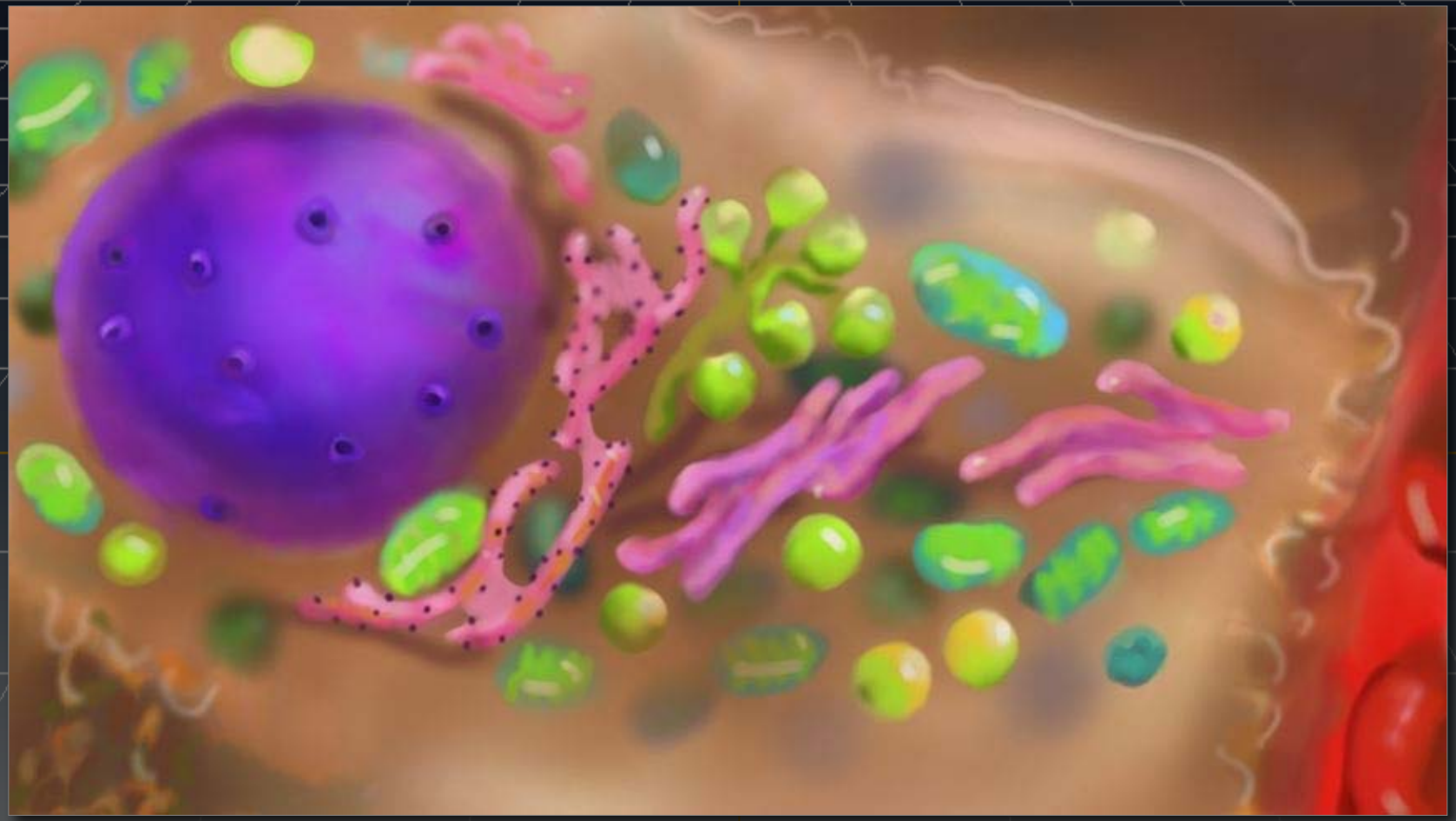
The small molecules will have a chalky surface that resembles the the initial APAP tablet. The various metabolites will have distinct colors to indicate different types.

Mood Board - Protein Structure

Concept Art

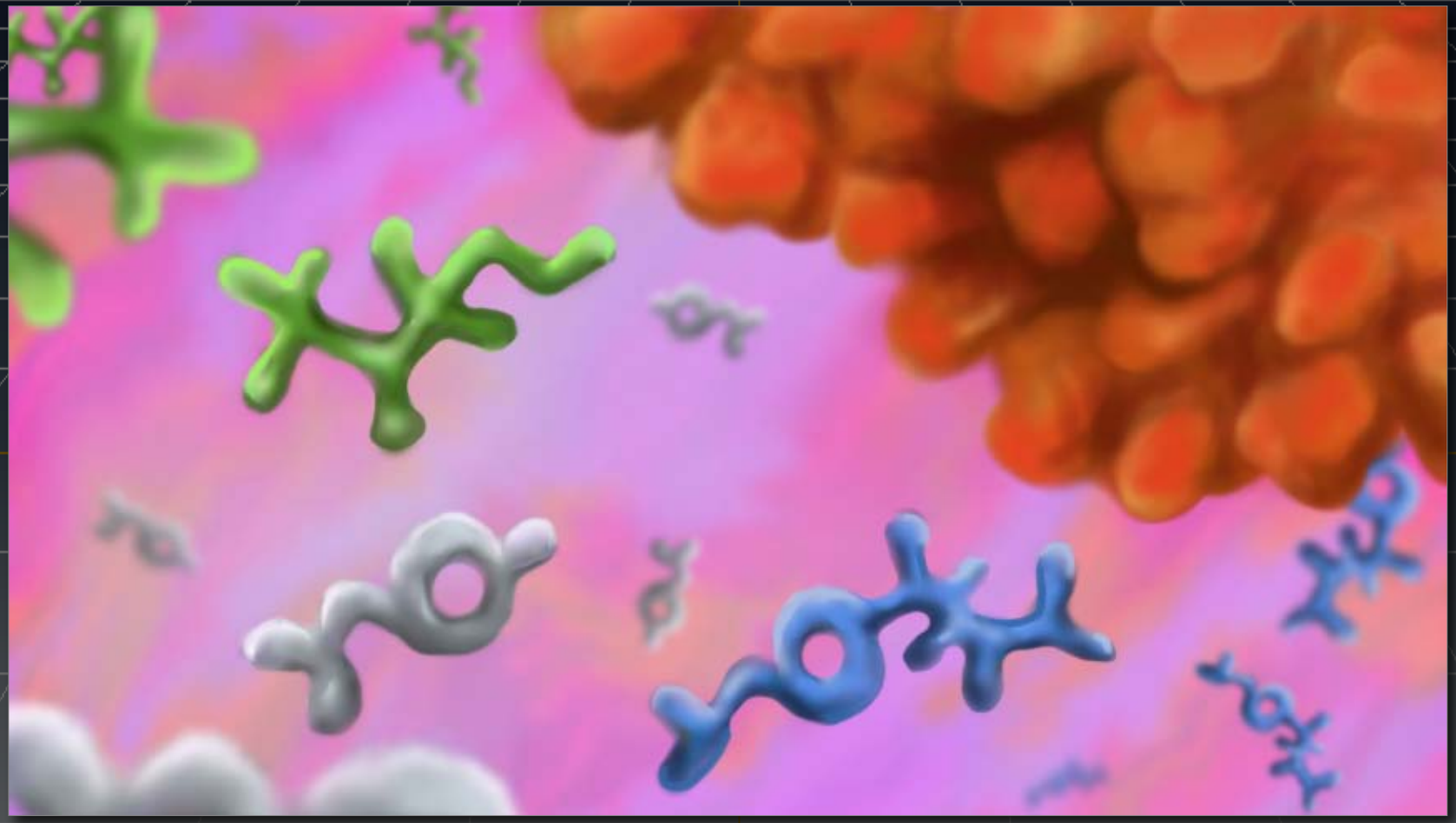
Liver Lobule

Concept Art



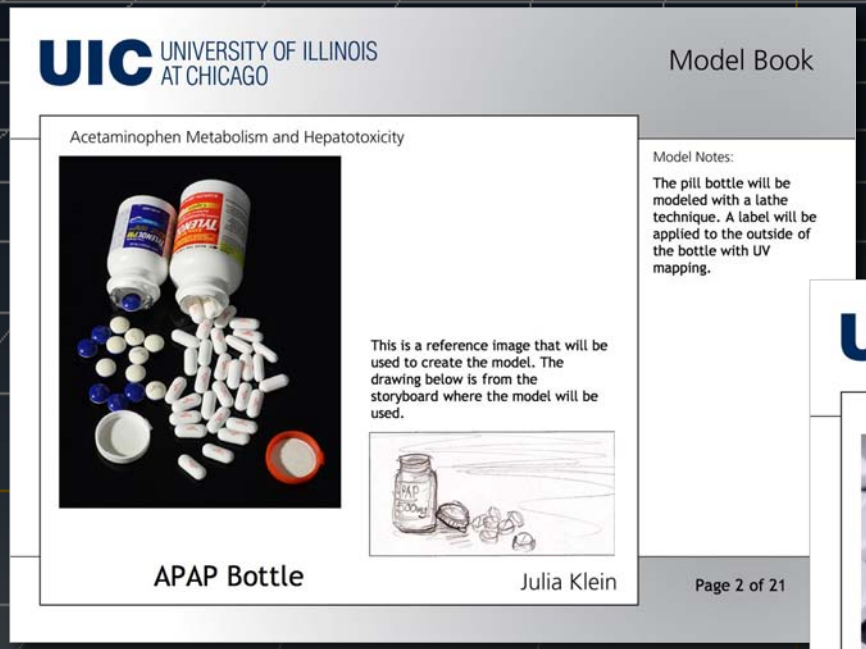
Hepatocyte

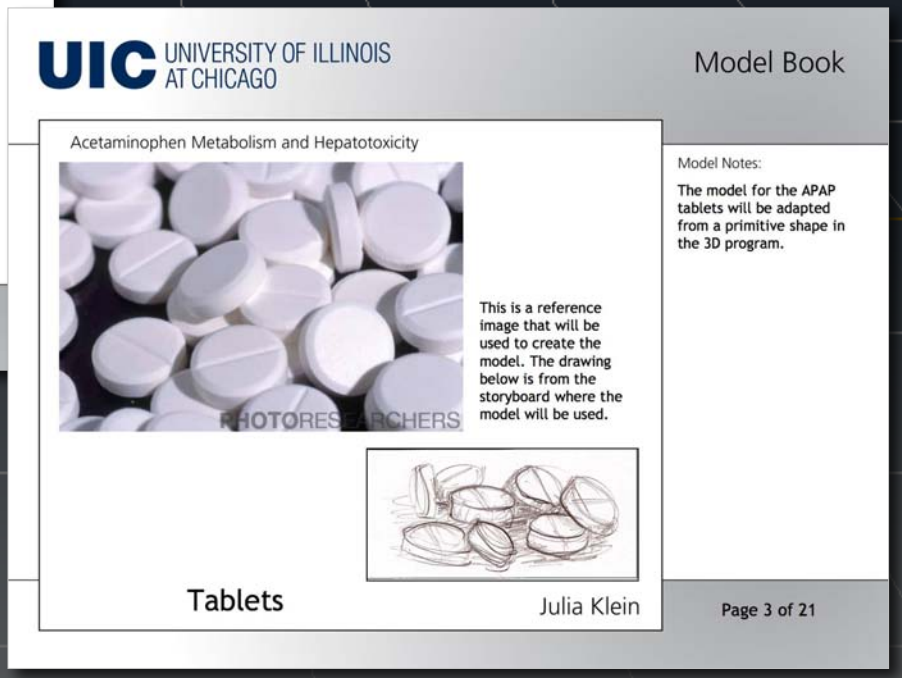
Concept Art



Intracellular Structures

Model Book

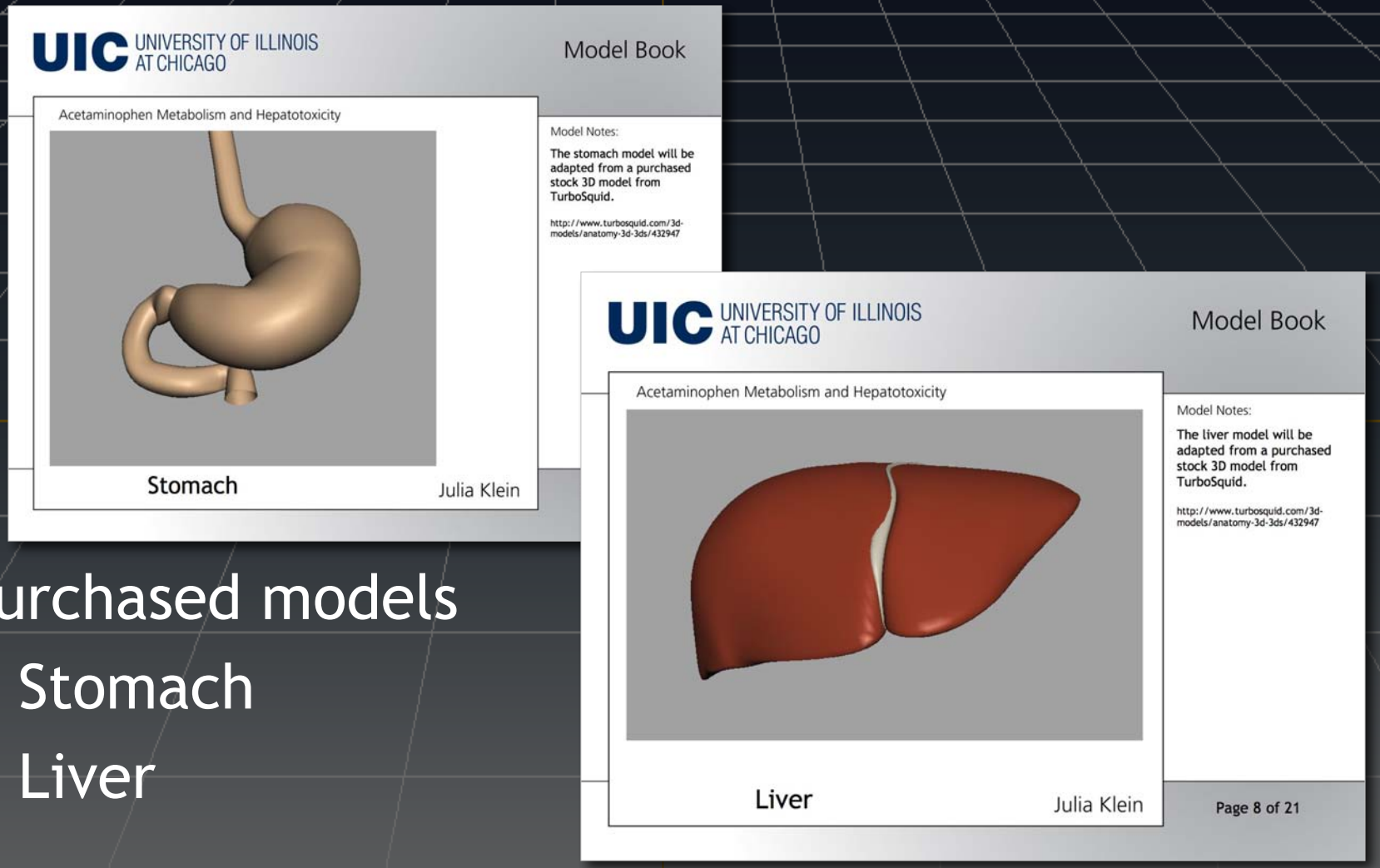




Acetaminophen models

- APAP bottle
- APAP tablets

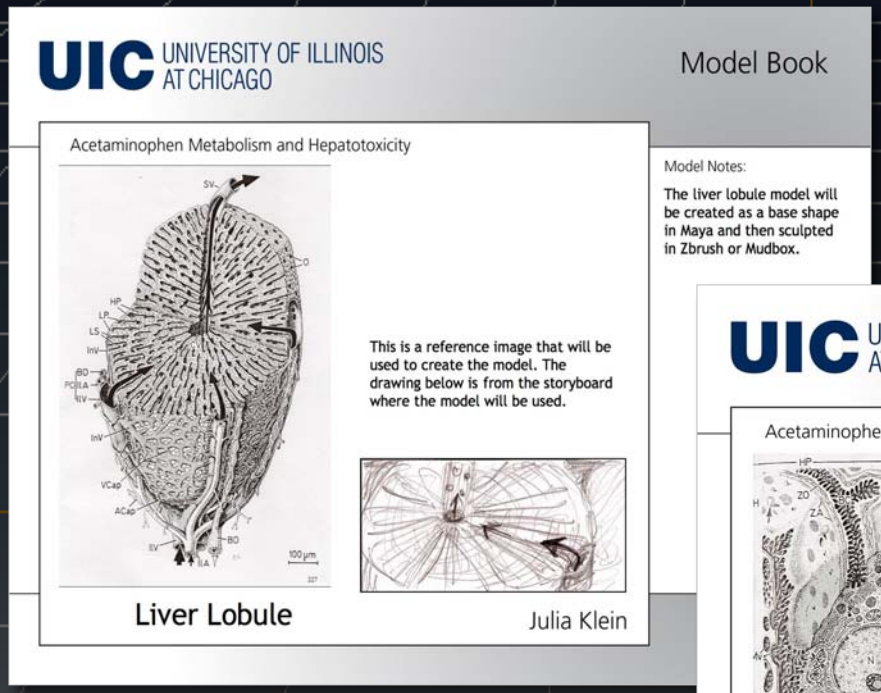
Model Book

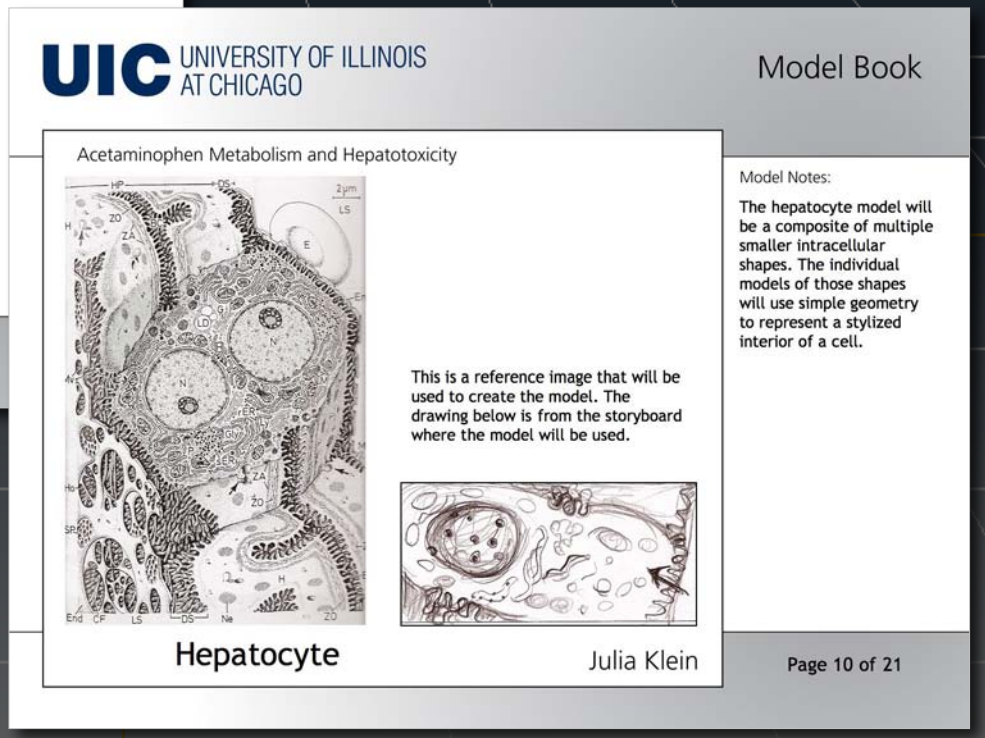


Purchased models

- Stomach
- Liver

Model Book

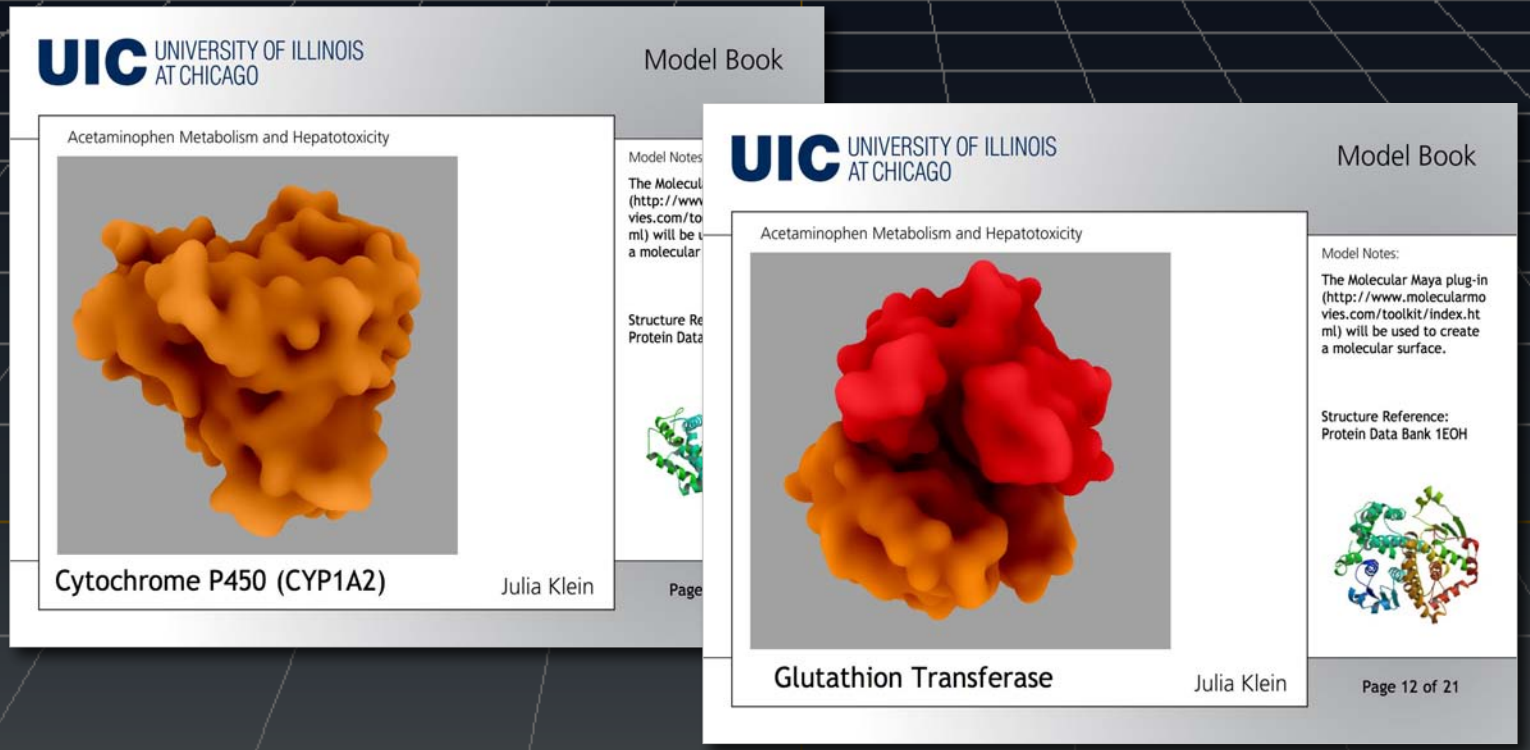




Sculpted models

- Liver Lobule
- Hepatocyte

Model Book



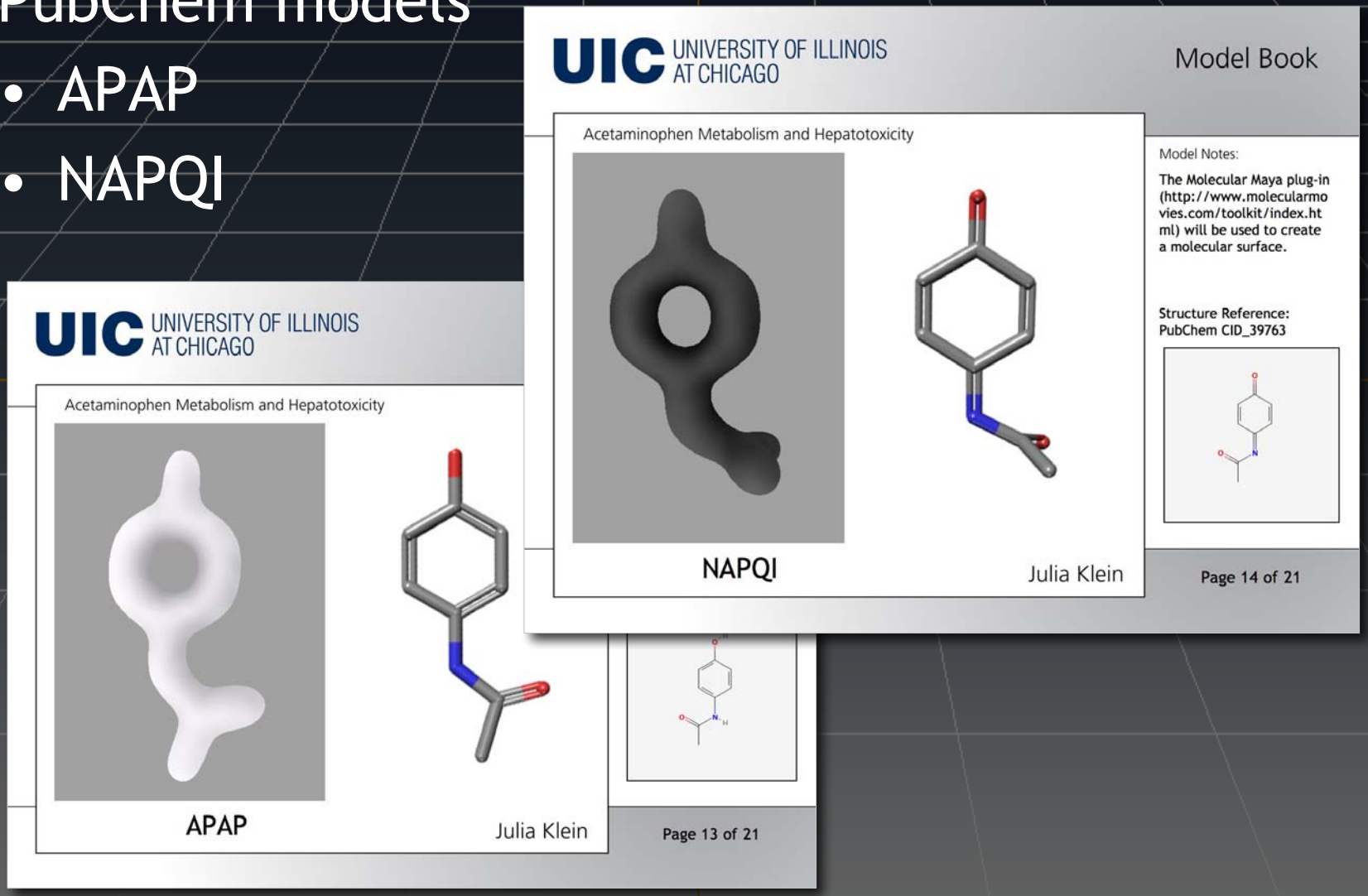
Protein Data Bank models

- Cytochrome P450
- Glutathione Transferase

Model Book

PubChem models

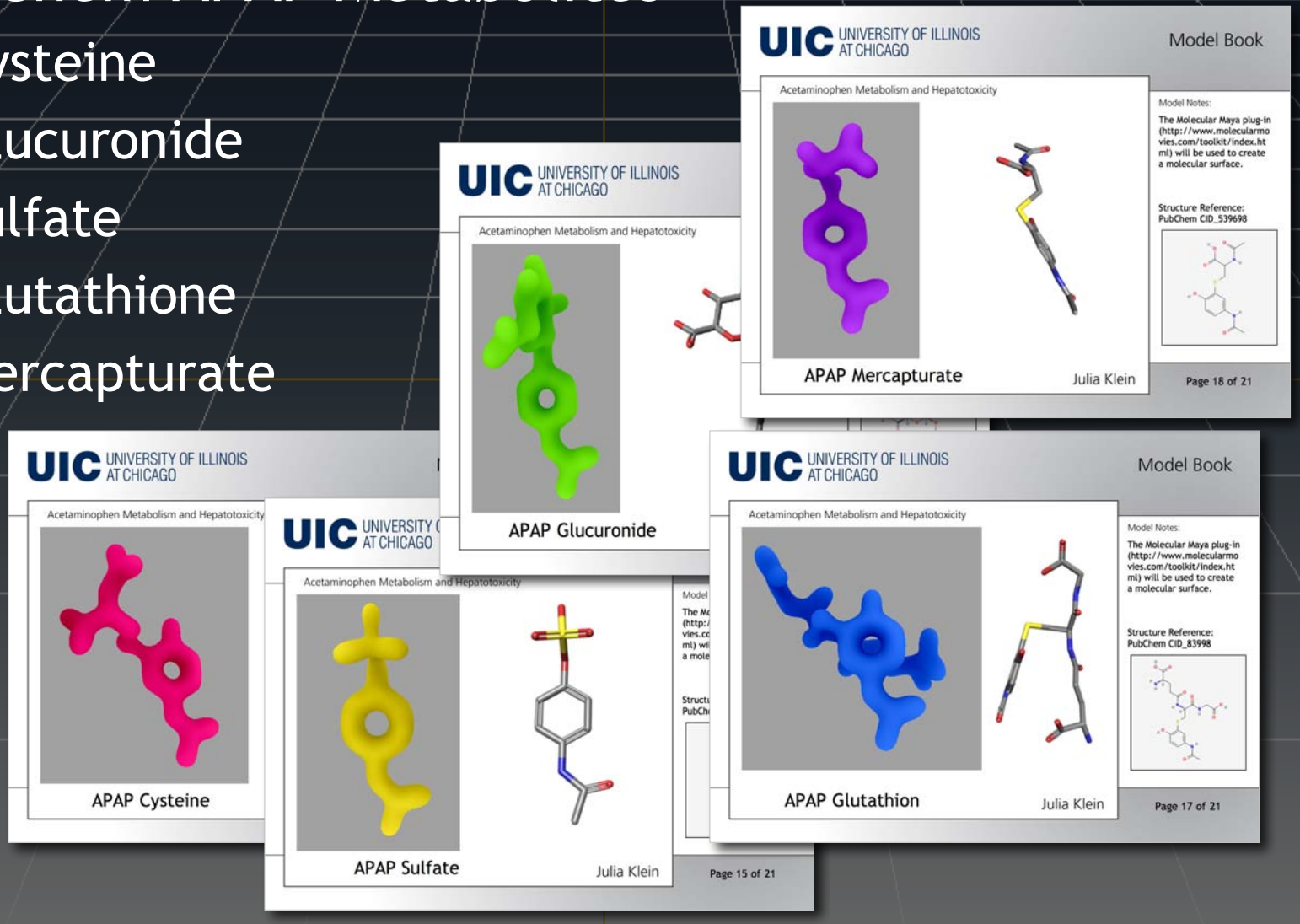
- APAP
- NAPQI



Model Book

PubChem APAP Metabolites

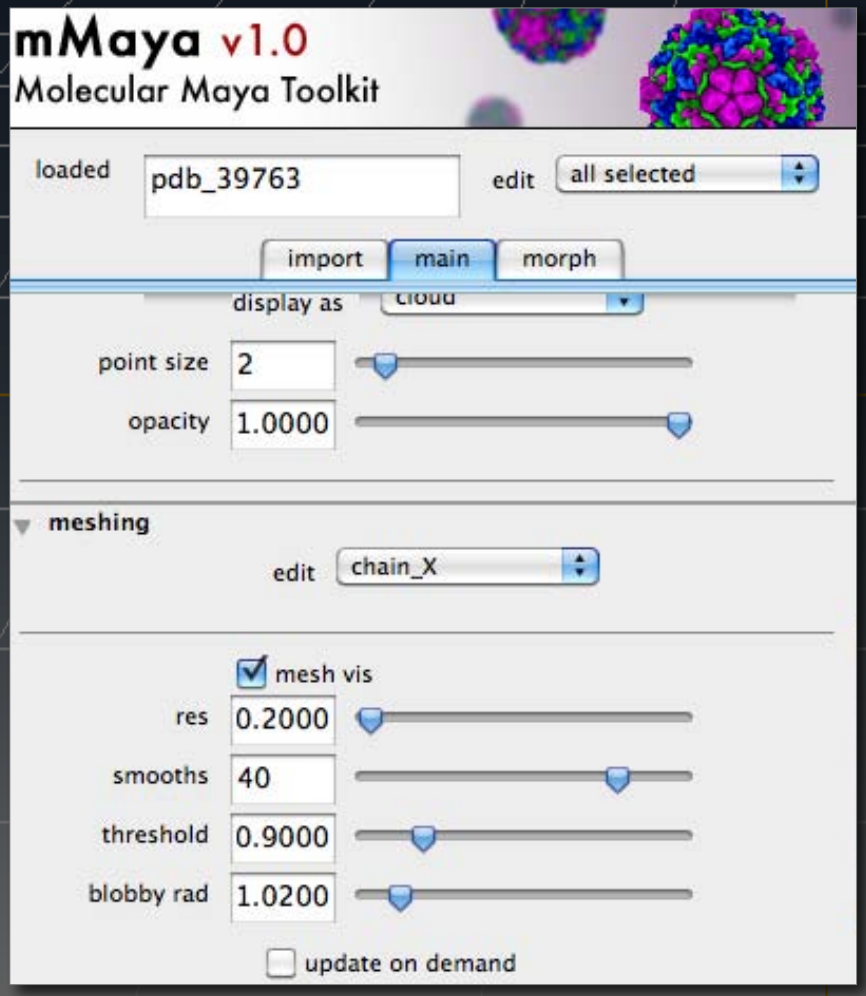
- Cysteine
- Glucuronide
- Sulfate
- Glutathione
- Mercapturate

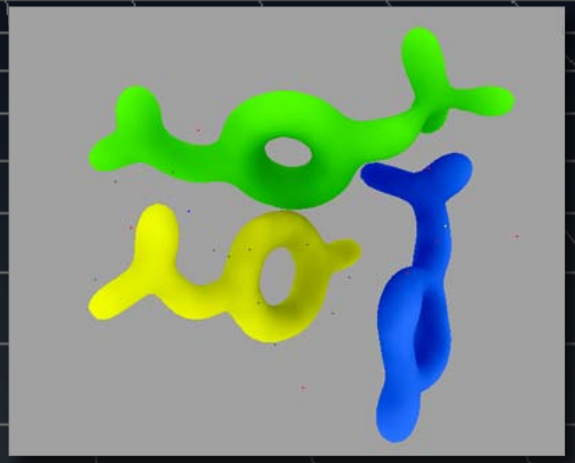


3D Modeling

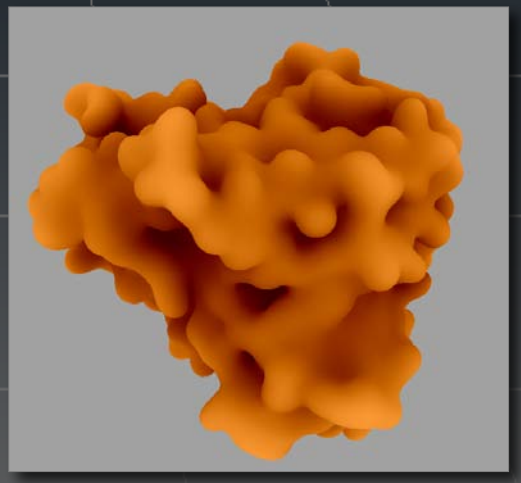
Molecular Maya (mMaya)

http://www.molecularmovies.com/toolkit/index.html





PubChem models

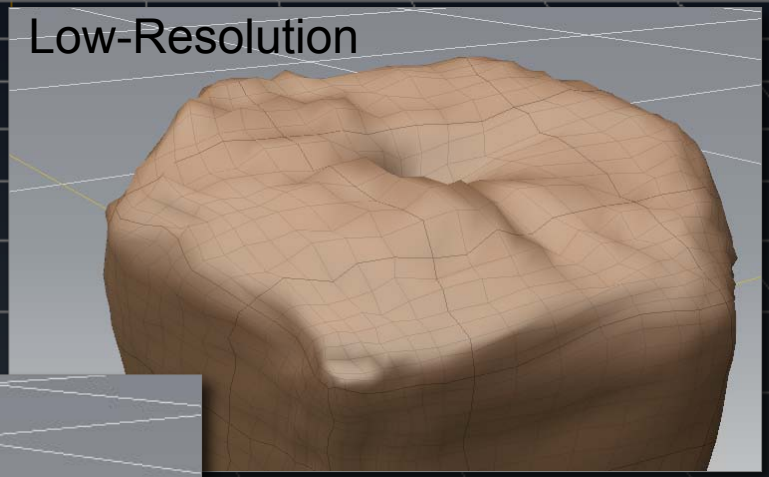


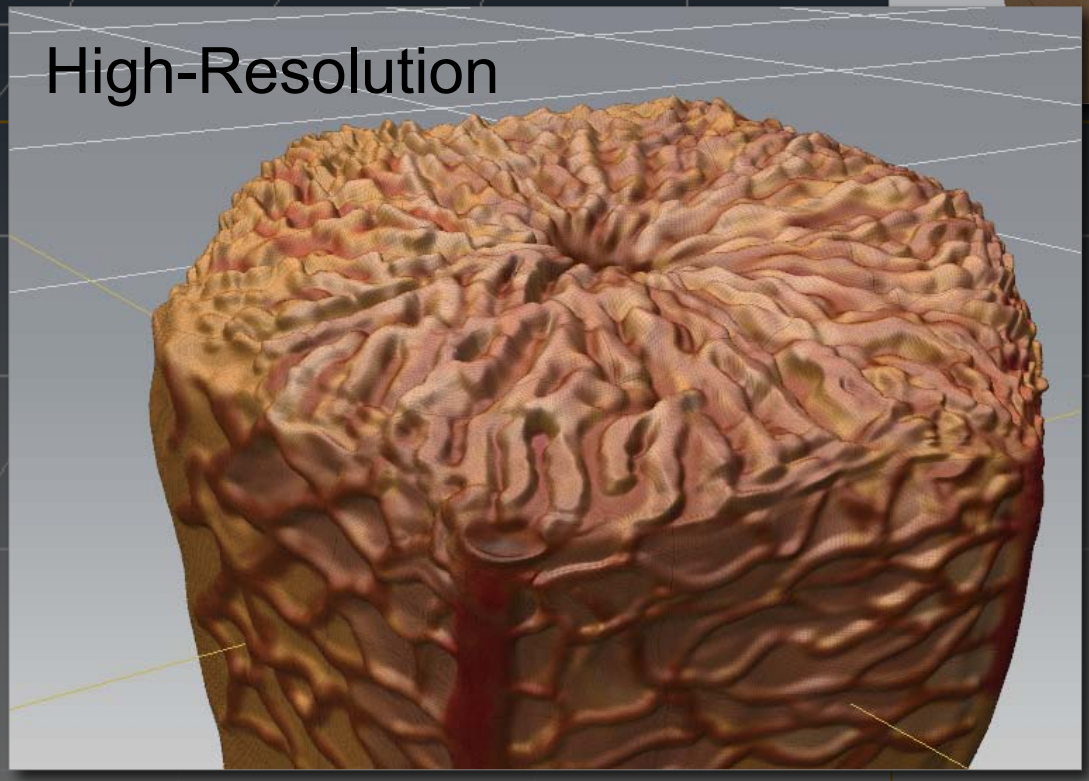
PDB model

3D Modeling

Mudbox® sculpting

- Liver lobule

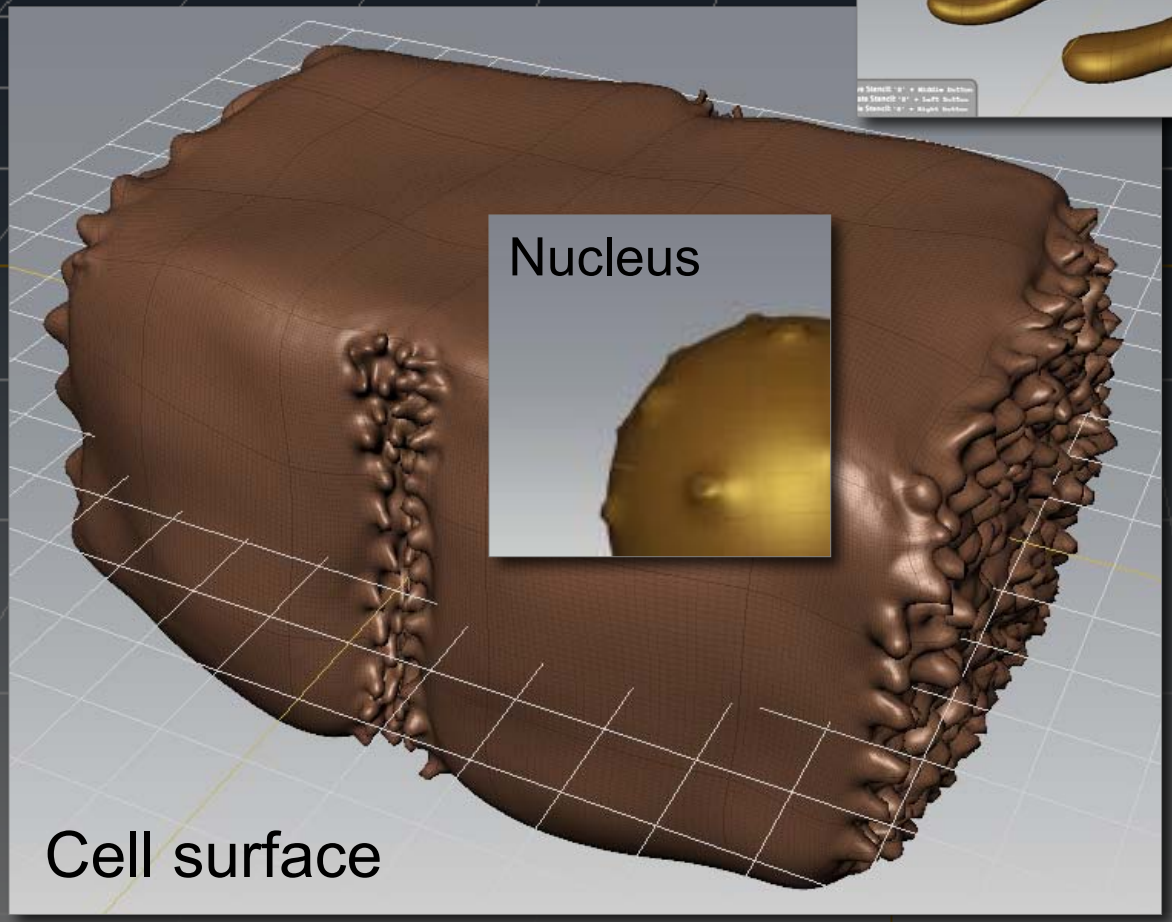




3D Modeling

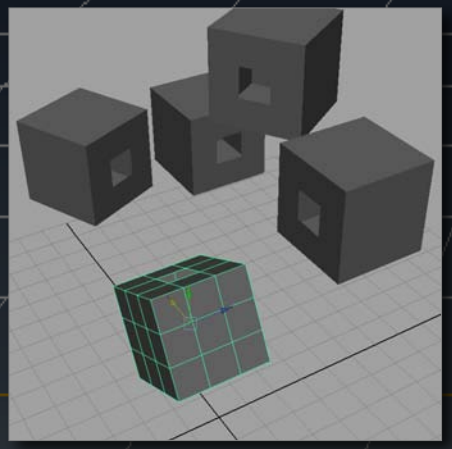
Mudbox® sculpting

- Hepatocyte

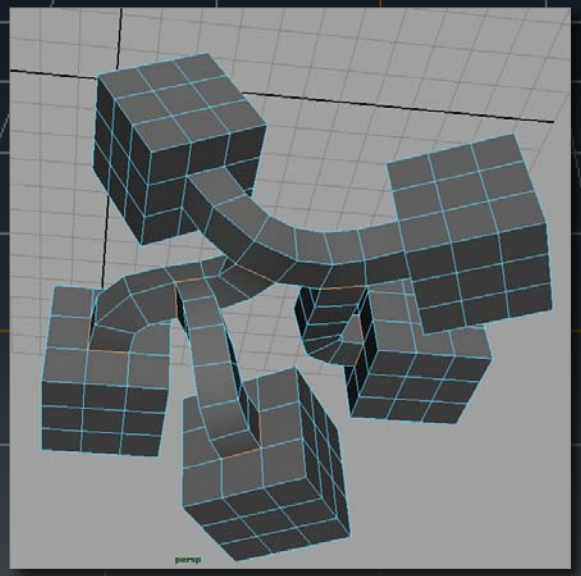


3D Modeling

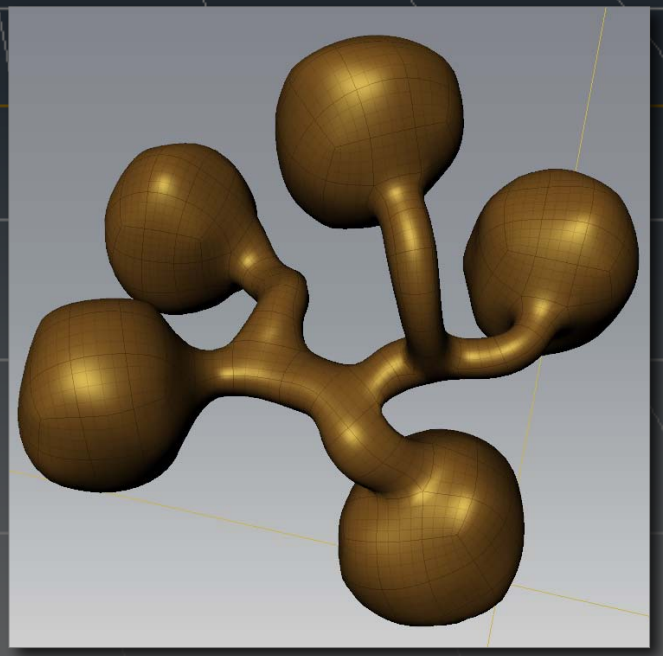
- Golgi apparatus



Primitive shapes



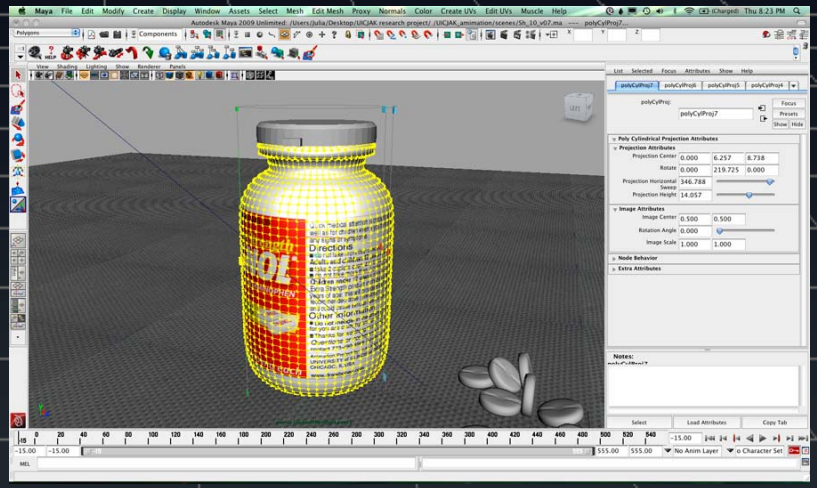
Connection



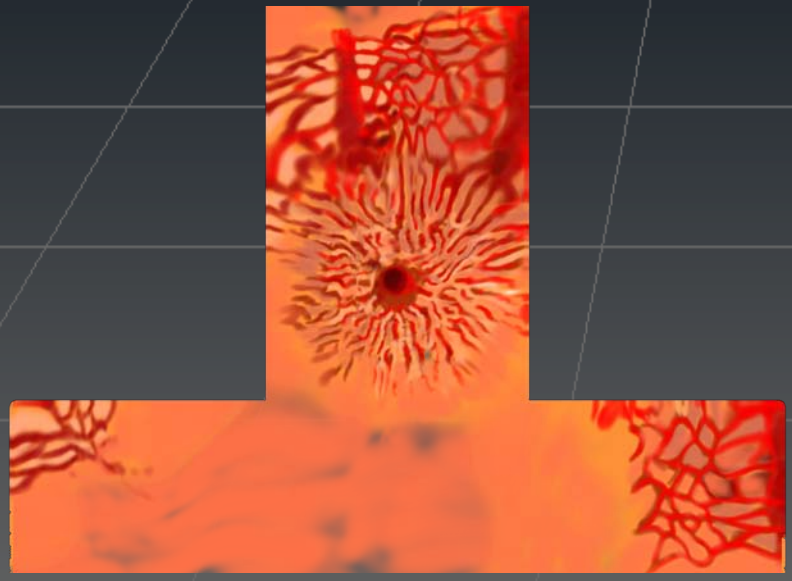
Smoothing

Texture and Lighting

Bottle label



UV Placement



Unwrapping

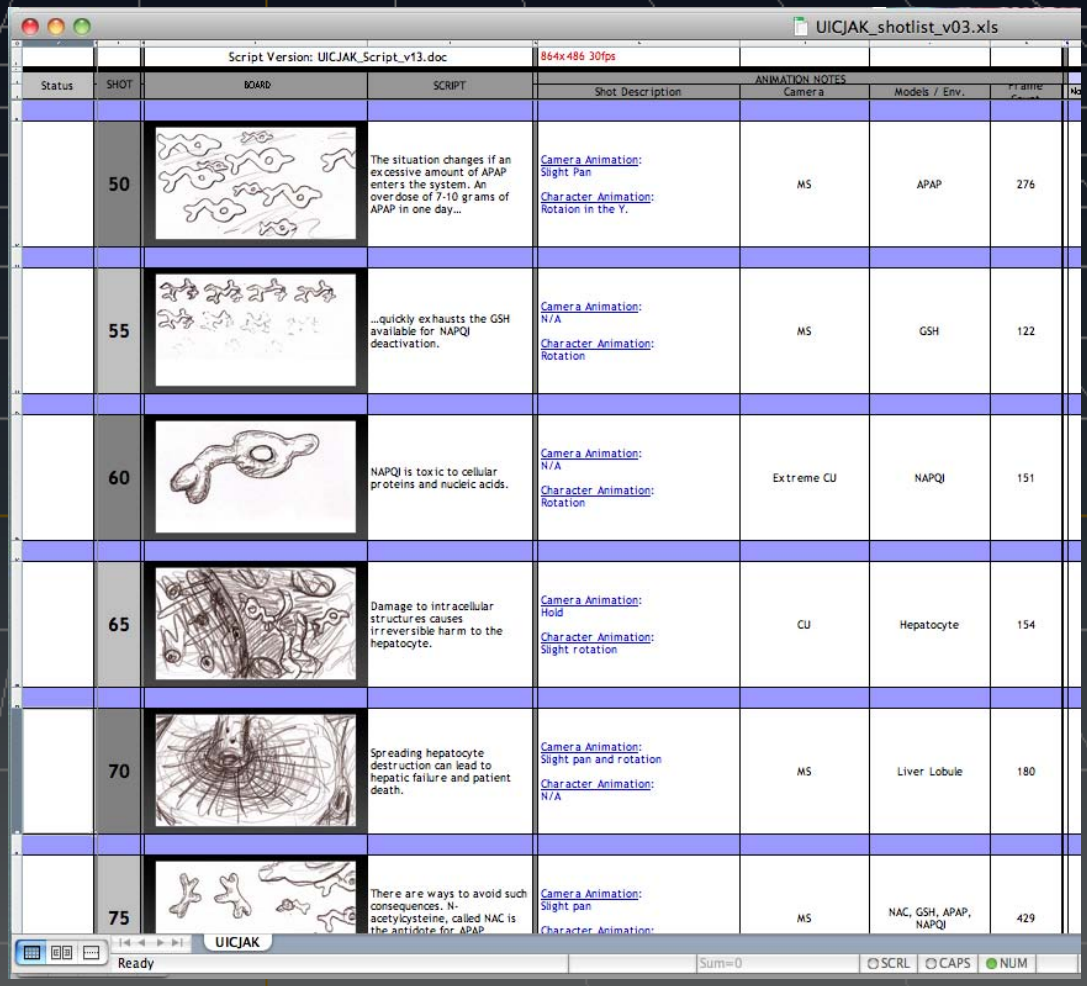
Final map paintings

Production

- Shot List
- 3D Animatic
- Rough Cut

Shot List

- Shot numbers
- Storyboards
- VO Script
- Labels
- Characters
- Shot lengths



UICJAK_shotlist_v03.xls

Script Version: UICJAK_Script_v13.doc | 864x486 30fps

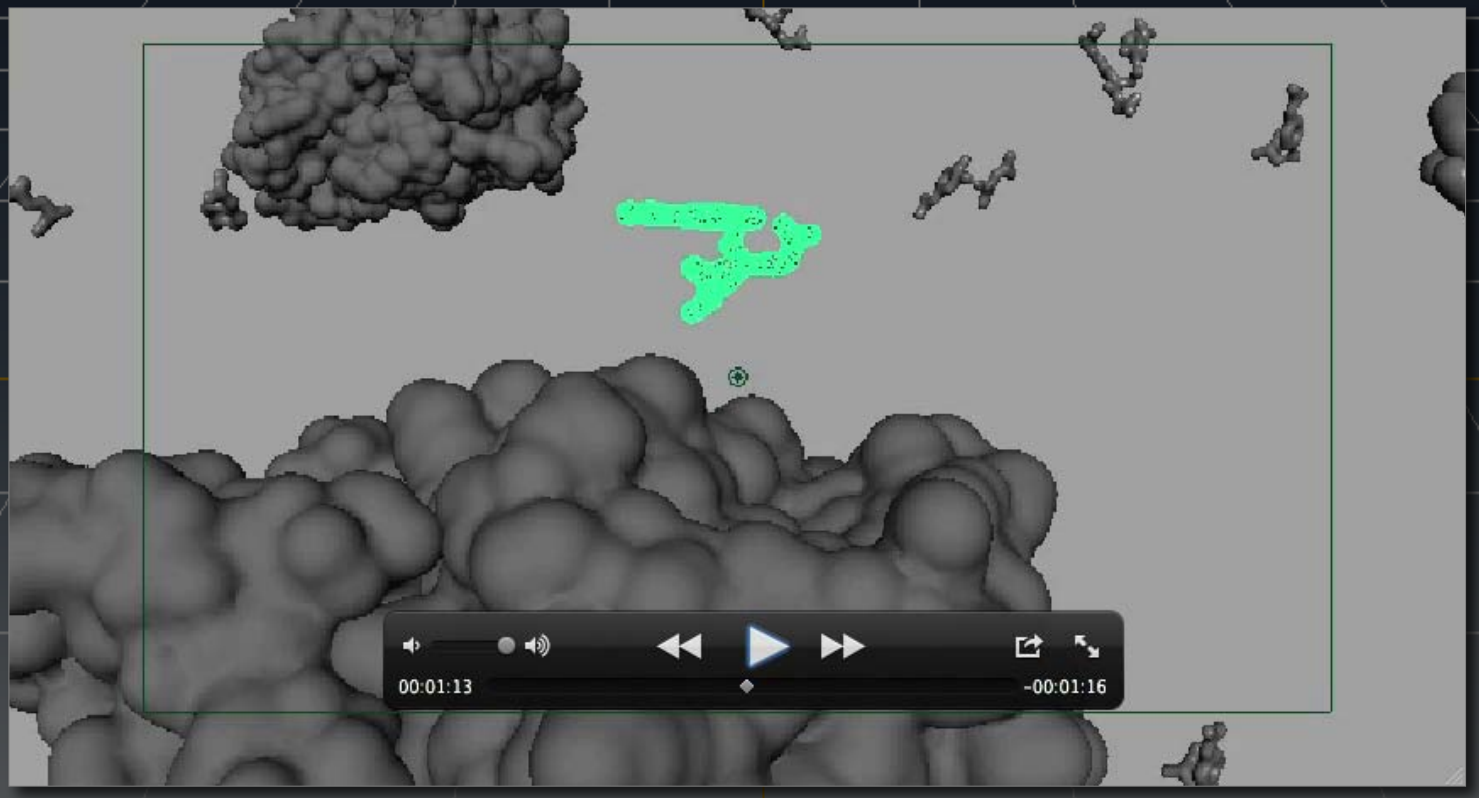
Status	SHOT	BOARD	SCRIPT	ANIMATION NOTES: Shot Description	Camera	Models / Env.	Frame Count
	50		The situation changes if an excessive amount of APAP enters the system. An overdose of 7-10 grams of APAP in one day...	Camera Animation: Slight Pan Character Animation: Rotaion in the Y.	MS	APAP	276
	55		...quickly exhausts the GSH available for NAPQI deactivation.	Camera Animation: N/A Character Animation: Rotation	MS	GSH	122
	60		NAPQI is toxic to cellular proteins and nucleic acids.	Camera Animation: N/A Character Animation: Rotation	Extreme CU	NAPQI	151
	65		Damage to intracellular structures causes irreversible harm to the hepatocyte.	Camera Animation: Hold Character Animation: Slight rotation	CU	Hepatocyte	154
	70		Spreading hepatocyte destruction can lead to hepatic failure and patient death.	Camera Animation: Slight pan and rotation Character Animation: N/A	MS	Liver Lobule	180
	75		There are ways to avoid such consequences. N-acetylcysteine, called NAC is the antidote for APAP	Camera Animation: Slight pan Character Animation:	MS	NAC, GSH, APAP, NAPQI	429

UICJAK

Ready | Sum=0 | SCRL | CAPS | NUM

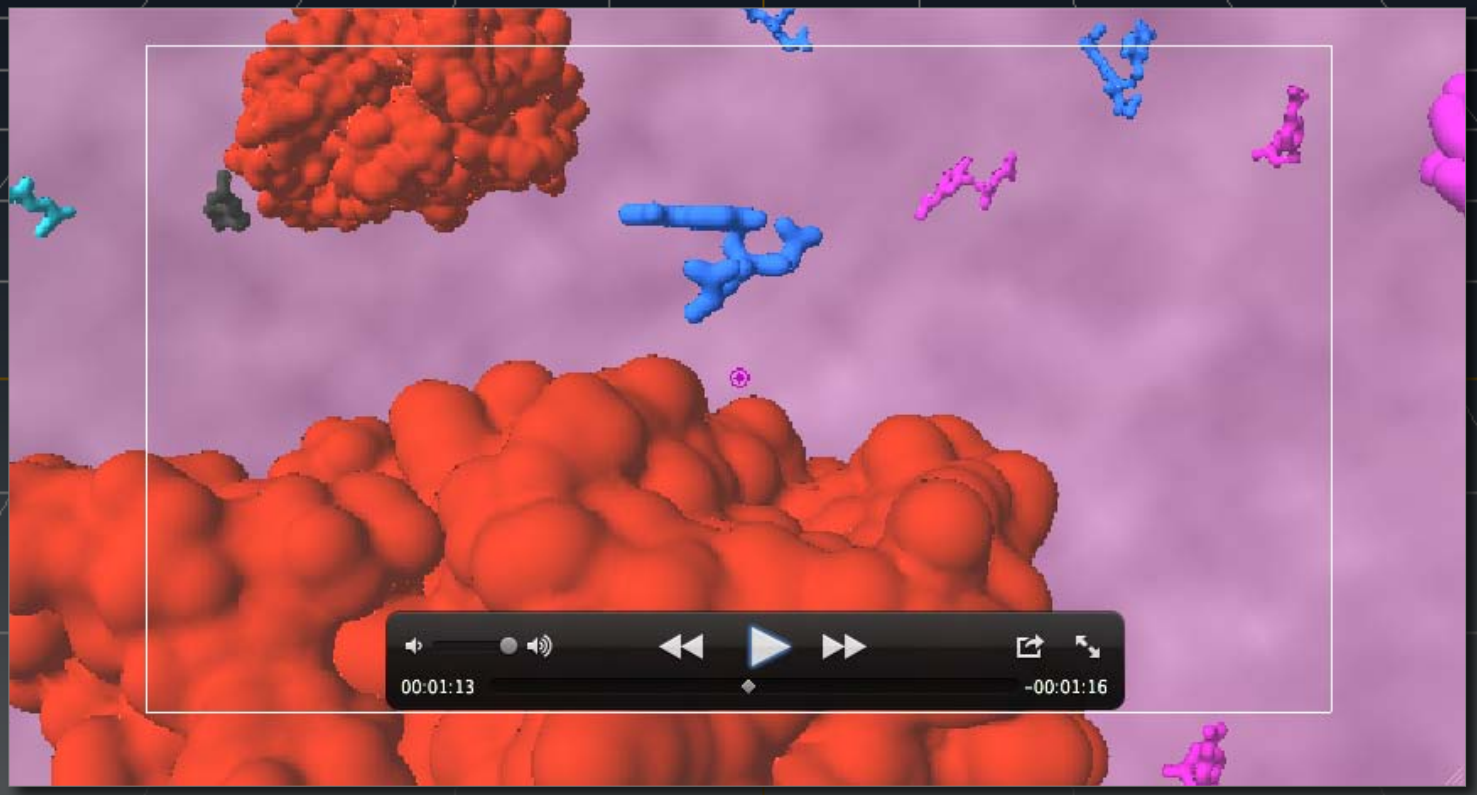
3D Animatic

- First pass movie with 3D models



Rough Cut

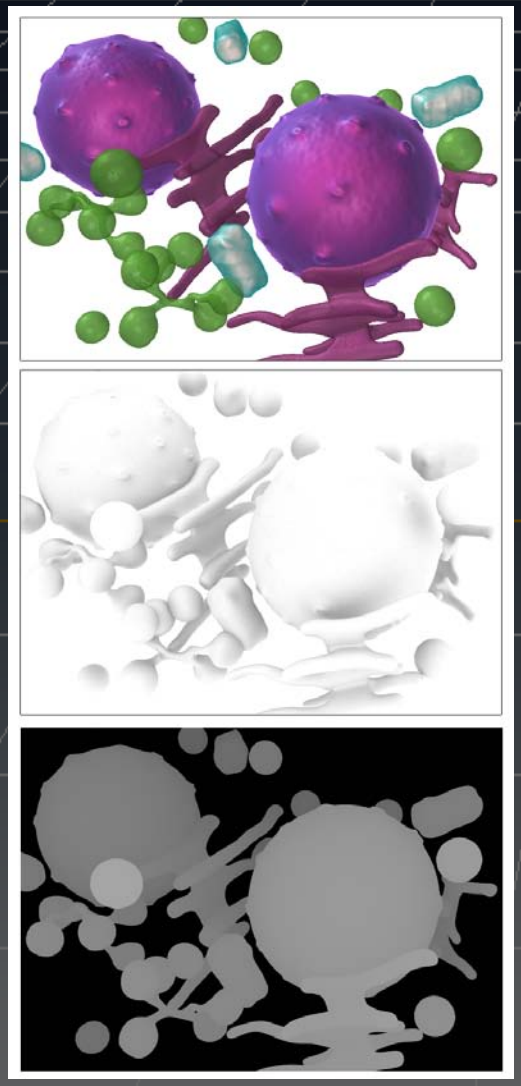
- Unrendered movie with final animation



Post-Production

- Rendering
- Compositing
- VO and music
- Final animation

Rendering

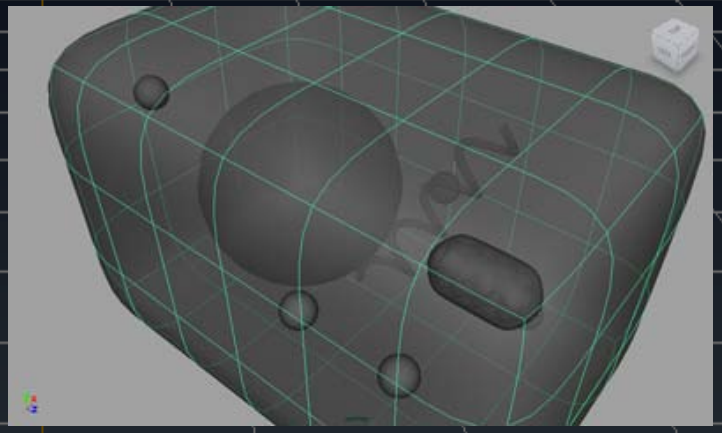


color

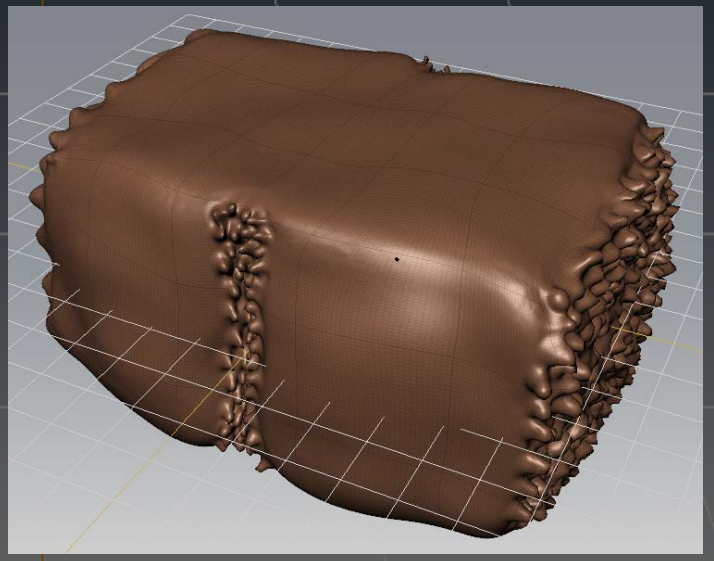
AO

depth

Render passes

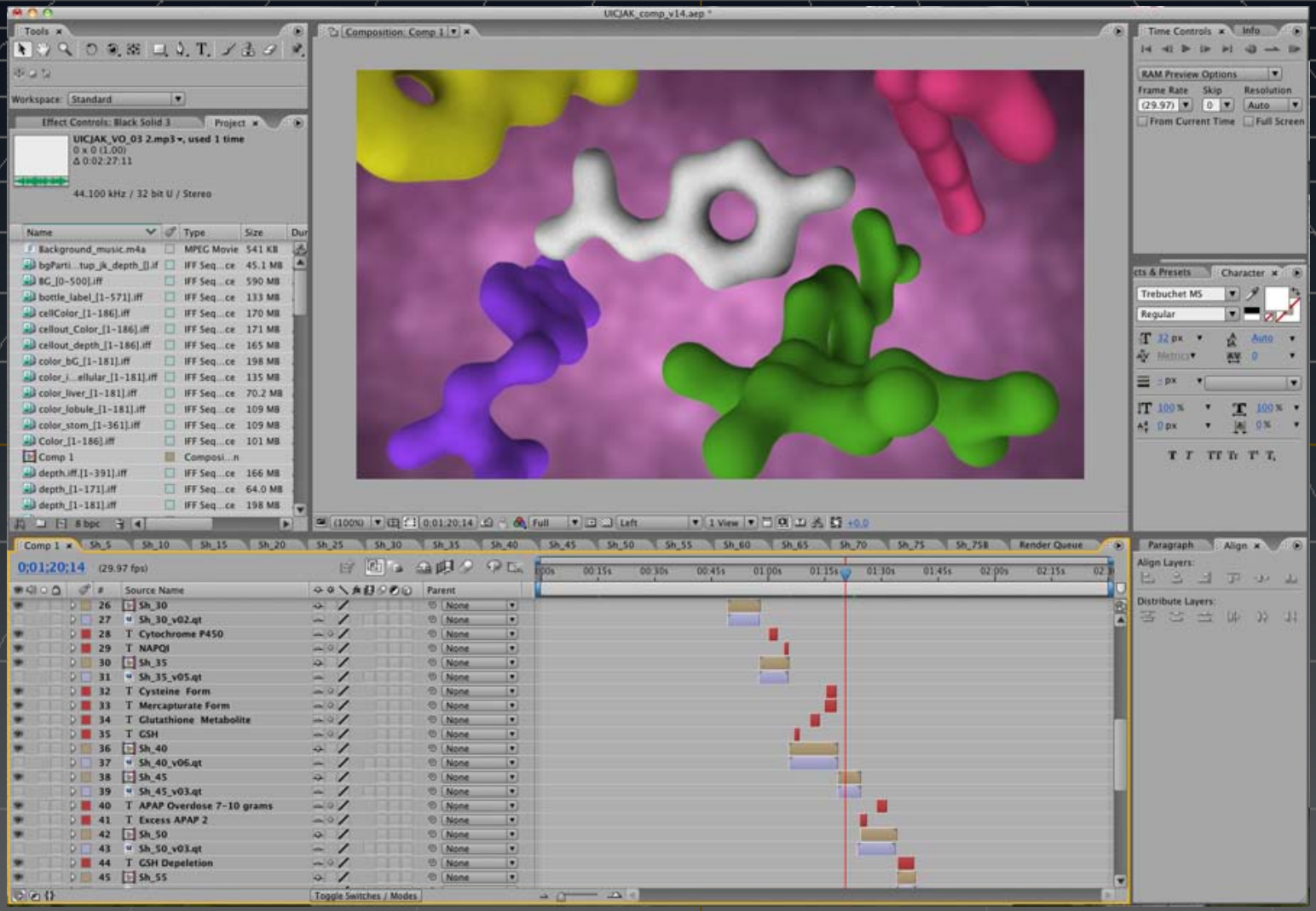


Swap low-resolution...



...for high-resolution

Compositing



Adobe After Effects

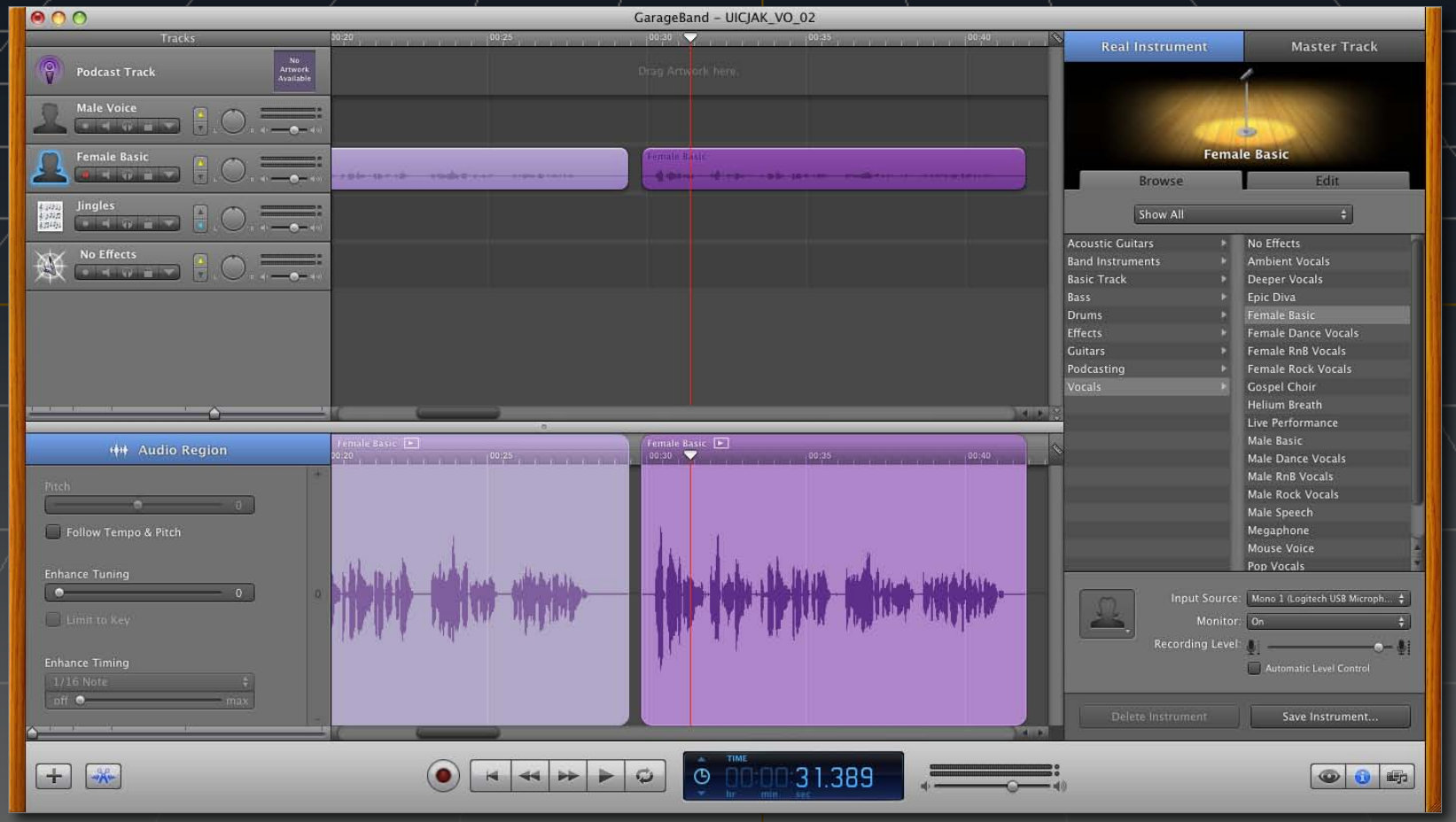
VO Recording -VO Script

- Pronunciation guide

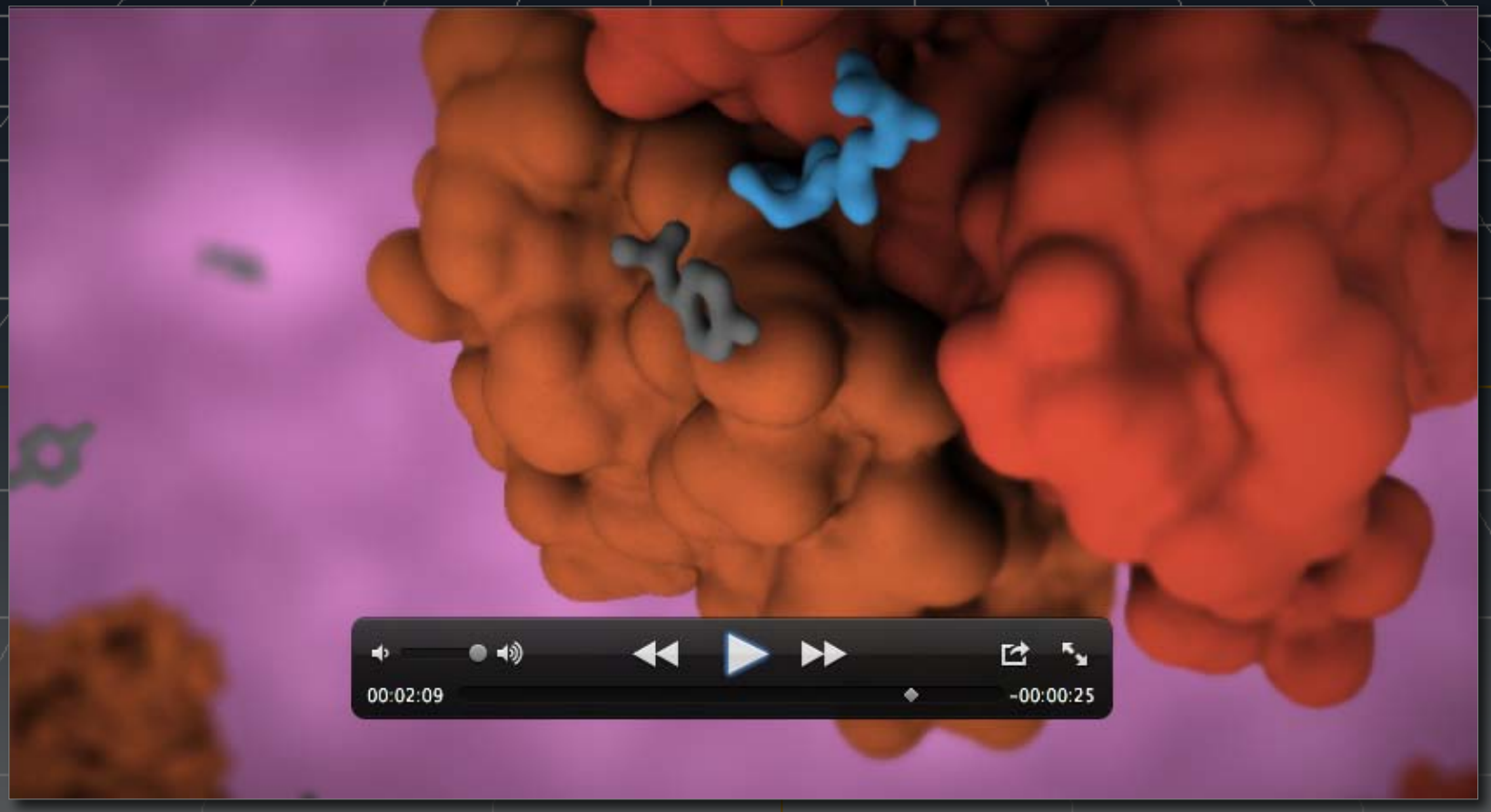
VO	Pronunciation Guide
Acetaminophen or APAP is a widely used medication with analgesic and antipyretic properties.	acet·amin·o·phen ə-ˌsē-tə-ˈmi-nə-fən, ˌa-sə-tə- an·al·ge·sic \-ˈjē-zik, -sik\ an·ti·py·ret·ic \-pī-ˈret-ik\
The FDA recommends a maximum dose of 4 grams of APAP per day. Consuming more APAP than recommended can potentially cause severe liver damage.	
When APAP is taken orally… …it absorbs rapidly in the upper GI tract.	
APAP enters the bloodstream and is carried to sites of action.	
The liver metabolizes APAP and produces metabolites required for function.	
Many metabolic pathways occur in the liver to rid excess APAP and other substances from the body.	
APAP is metabolized in the hepatocyte's smooth endoplasmic reticulum.	he·pa·to·cyte hi-ˈpat-ə-ˌsīt en·do·plas·mic ˌen-də-ˈplaz-mik re·tic·u·lum ri-ˈtik-yə-ləm
The majority of APAP… …is conjugated by enzymes into inert sulfate and glucuronide metabolites.	sul·fate ˈsəl-ˌfāt gluc·uro·nide glü-ˈkyur-ə-ˌnīd
An enzyme, cytochrome P450, converts the remaining APAP… …to NAPQI.	cy·to·chrome ˈsīt-ə-ˌkrōm P four fifty
NAPQI can be combined with GSH… …to create an intermediate glutathione metabolite. Further conjugation results in mercapturate and cysteine forms.	glu·ta·thi·one ˌglüt-ə-ˈthī-ˌōn mer-cap-TUR-ate cys·teine ˈsis-tə-ˌēn

VO Recording

- Apple Garage Band
- Podcast recording settings



Final Animation

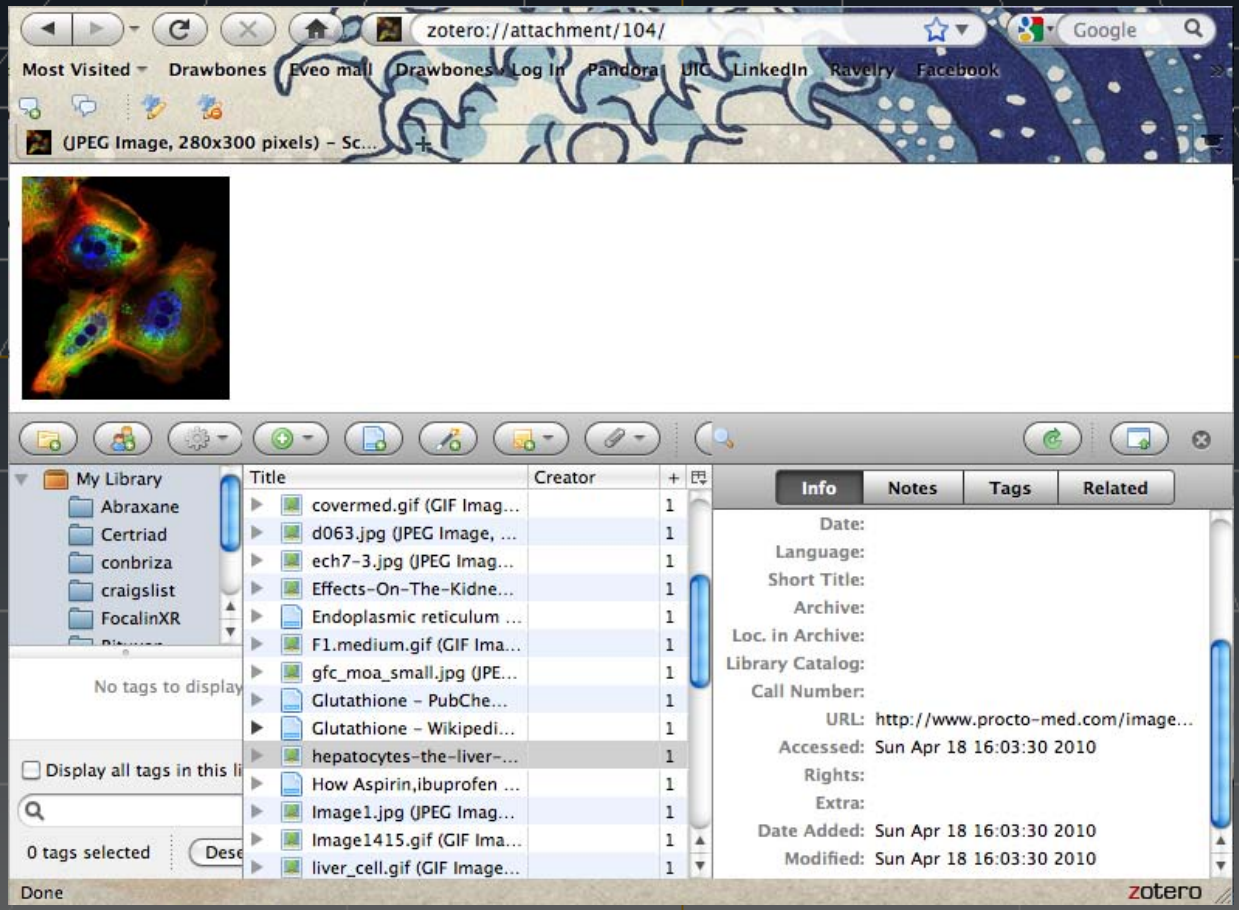


Project Management

How to organize a project!

Zotero http://www.zotero.org/

- Tracker of online references and images

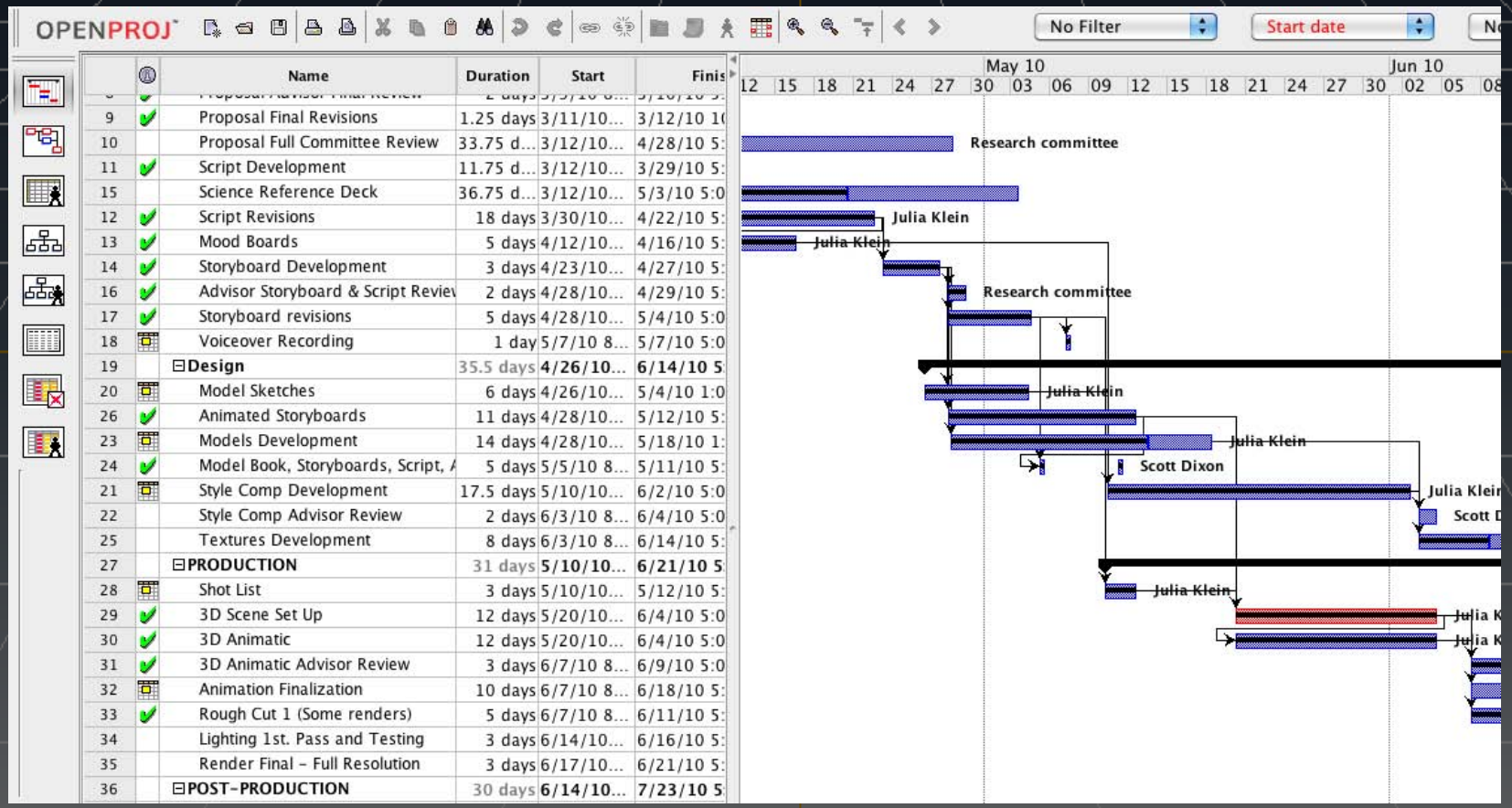


Papers http://mekentosj.com/papers/

- PDF organizer and search tool

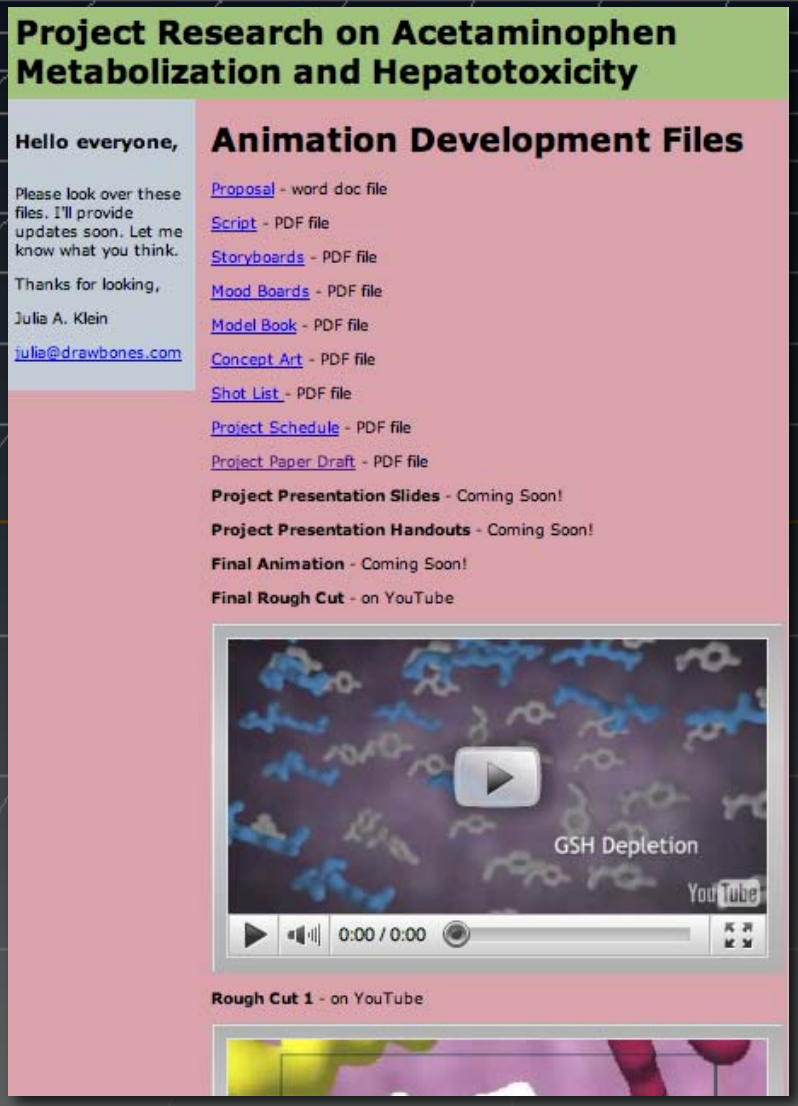
OpenProj http://openproj.org/

- Timeline manager



		Name	Duration	Start	Finis
9	✓	Proposal Final Revisions	1.25 days	3/11/10...	3/12/10 1(
10		Proposal Full Committee Review	33.75 d...	3/12/10...	4/28/10 5:
11	✓	Script Development	11.75 d...	3/12/10...	3/29/10 5:
15		Science Reference Deck	36.75 d...	3/12/10...	5/3/10 5:0
12	✓	Script Revisions	18 days	3/30/10...	4/22/10 5:
13	✓	Mood Boards	5 days	4/12/10...	4/16/10 5:
14	✓	Storyboard Development	3 days	4/23/10...	4/27/10 5:
16	✓	Advisor Storyboard & Script Revie\	2 days	4/28/10...	4/29/10 5:
17	✓	Storyboard revisions	5 days	4/28/10...	5/4/10 5:0
18		Voiceover Recording	1 day	5/7/10 8...	5/7/10 5:0
19		⊟**Design**	35.5 days	**4/26/10...**	**6/14/10 5**
20		Model Sketches	6 days	4/26/10...	5/4/10 1:0
26	✓	Animated Storyboards	11 days	4/28/10...	5/12/10 5:
23		Models Development	14 days	4/28/10...	5/18/10 1:
24	✓	Model Book, Storyboards, Script, A	5 days	5/5/10 8...	5/11/10 5:
21		Style Comp Development	17.5 days	5/10/10...	6/2/10 5:0
22		Style Comp Advisor Review	2 days	6/3/10 8...	6/4/10 5:0
25		Textures Development	8 days	6/3/10 8...	6/14/10 5:
27		⊟**PRODUCTION**	31 days	**5/10/10...**	**6/21/10 5**
28		Shot List	3 days	5/10/10...	5/12/10 5:
29	✓	3D Scene Set Up	12 days	5/20/10...	6/4/10 5:0
30	✓	3D Animatic	12 days	5/20/10...	6/4/10 5:0
31	✓	3D Animatic Advisor Review	3 days	6/7/10 8...	6/9/10 5:0
32		Animation Finalization	10 days	6/7/10 8...	6/18/10 5:
33	✓	Rough Cut 1 (Some renders)	5 days	6/7/10 8...	6/11/10 5:
34		Lighting 1st. Pass and Testing	3 days	6/14/10...	6/16/10 5:
35		Render Final – Full Resolution	3 days	6/17/10...	6/21/10 5:
36		⊟**POST-PRODUCTION**	30 days	**6/14/10...**	**7/23/10 5**

Project Website http://www.drawbones.com/UICJAK/



- Created to organize project files
- Links to YouTube
- Will be updated as new progress is made

Conclusions

- An animation was created that visually explains the APAP metabolic pathway and its potential for hepatotoxicity
- Project research provided a level of detail appropriate for an audience of healthcare providers
- Production roles and steps from a professional medical animation workflow were consolidated and successfully performed by one researcher

Thanks!

- Eveo medical animation team
  - Baron, Dario, Erich, Fred, Henry, Kevin, Sara, Rick, Bob, Carly, Paul, Nicole, Monica and many others
- Fred Meyer Pharmacy
  - Pharmacists
  - Pharmacy technicians
- Research committee members
  - Scott Dixon
  - John Daugherty
  - Scott Barrows
- Tim Stack
- Carol Babin
- Everyone else who encouraged this project along the way

Questions?

julia@drawbones.com

http://www.drawbones.com/UICJAK/