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MYELOMA INSTITUTE FOR RESEARCH AND THERAPY

UNIVERSITY OF ARKANSAS FOR MEDICAL SCIENCES

Profiling Multiple Myeloma Engraftment Phenomena via an *in-vivo* SCID Mouse Model and RNA-seq

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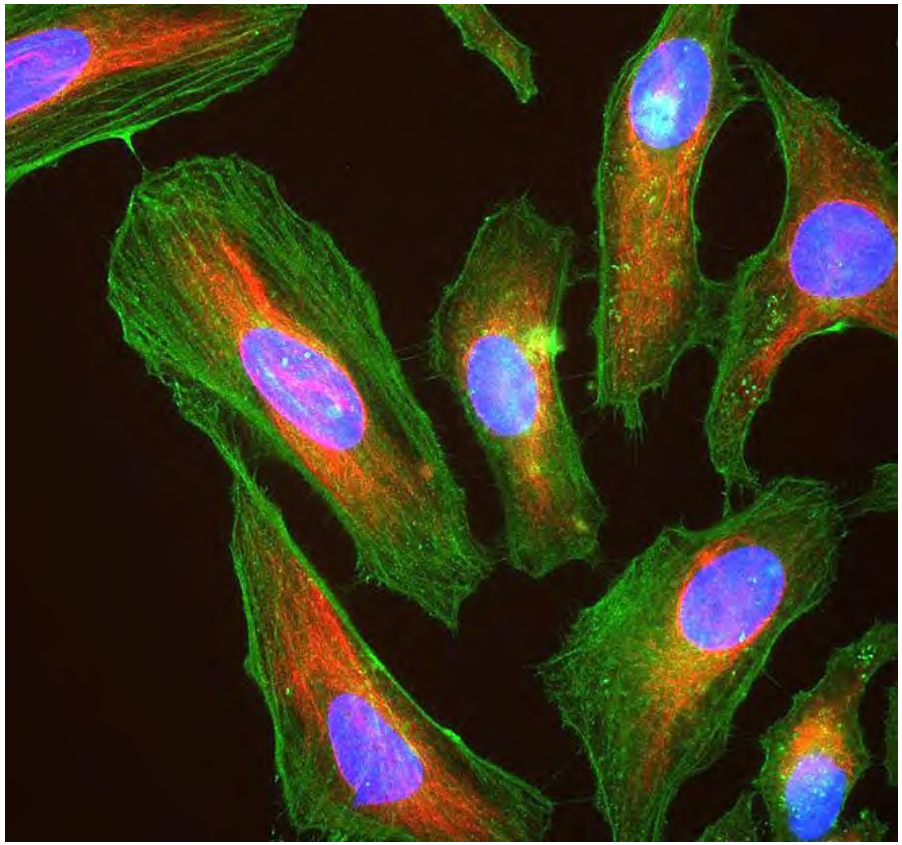
Why use models in cancer research?

- What is a cancer disease model?
  - Cells in a dish
  - Animals (sometimes modified)
    - Mouse, Rat, Zebra fish, Rabbit, Hamster
- Majority of cancers are not curable or medically managed well
- Why do we need cancer models?
  - Drugs, diagnostics, R&D

Cells in a petri-dish : Hela Cell Line (1950s)

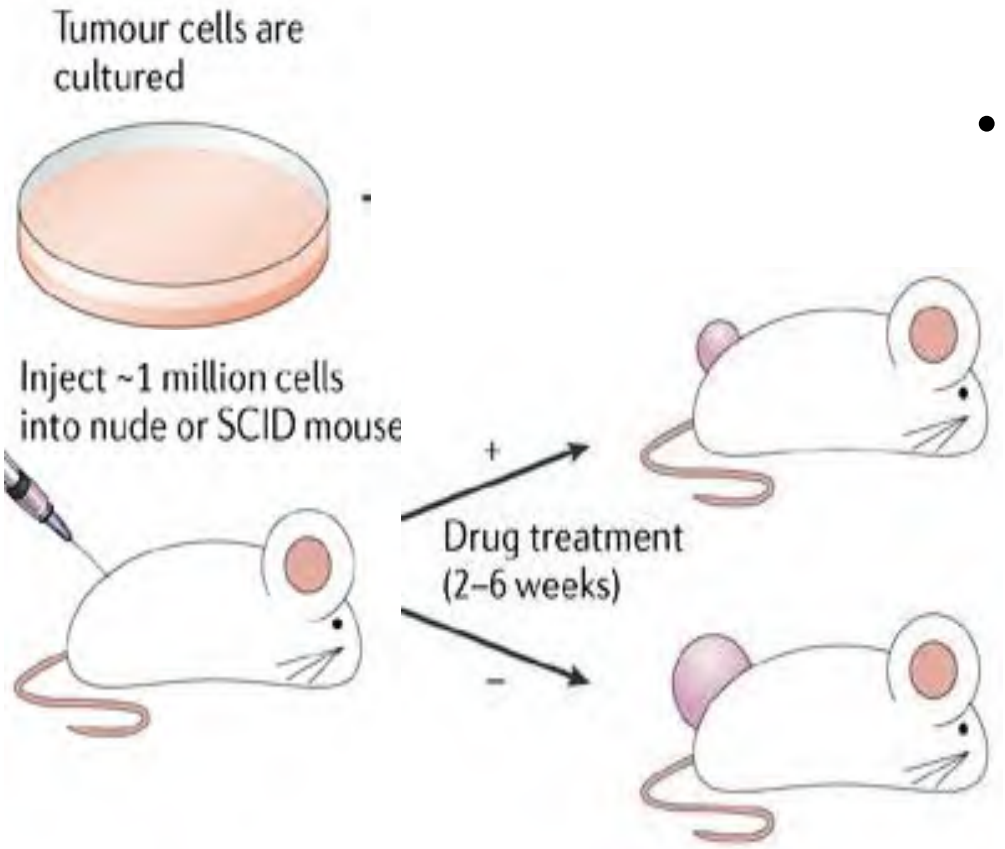


HeLa cells stained with antibody to actin (green), vimentin (red) and DNA (blue). Image courtesy of EnCor Biotechnology Inc.

- Cervical Cancer cells from a patient
- Proliferate rapidly
- Testing compounds /drugs
- Disadvantages: Lack of microenvironment

Laboratory mouse (*mus musculus*) cancer models (1980s):

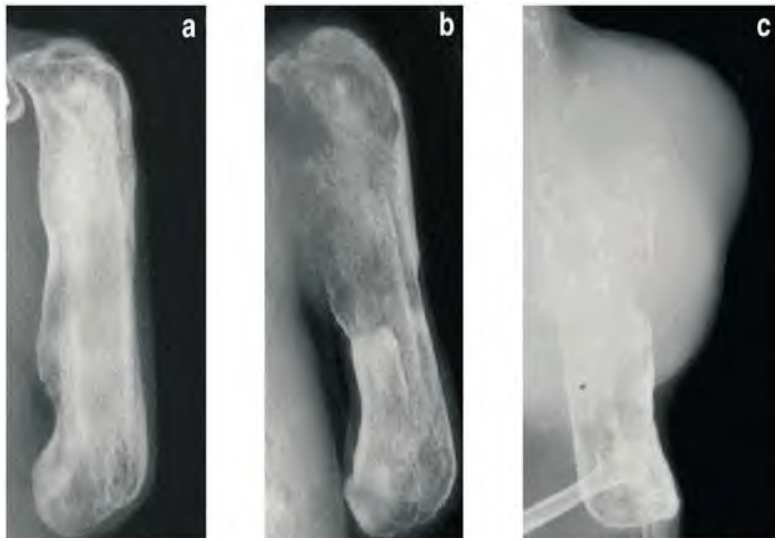
Drug testing in mice models

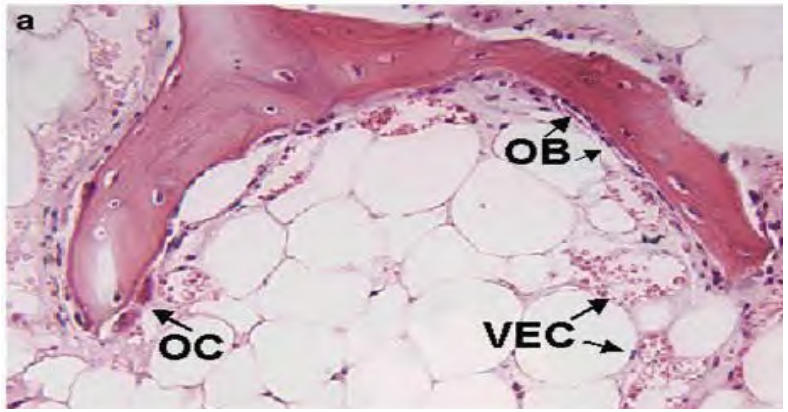


- "Microenvironment"
- Similarities to humans
  - Protein coding regions are 85% identical
  - Physiological
  - Molecular

Mice model for multiple myeloma

- Multiple myeloma (MM) is a type of plasma cell malignancy
- **SCID-hu myeloma model =** SCID-hu mouse + human fetal bone + myeloma patient plasma cells
- Ethical concerns for use of human fetal bones in SCID-Hu model
- **SCID-rab myeloma model =** SCID-hu mouse + ***Rabbit bone +*** myeloma patient plasma cells





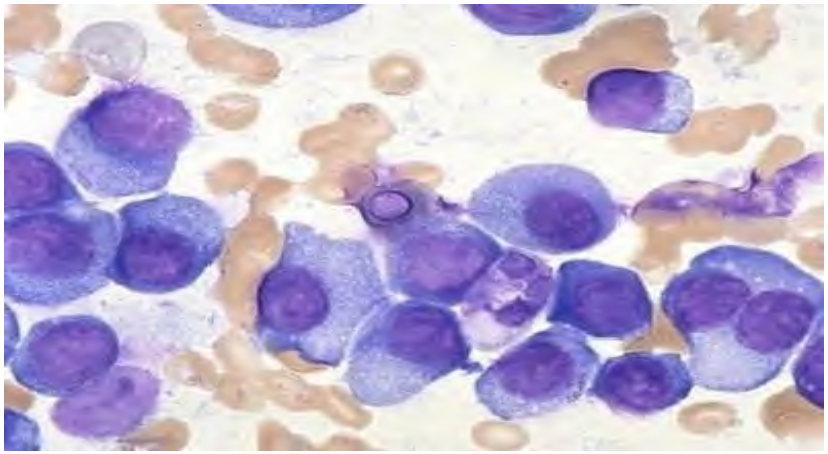
Yaccoby S. et al, 1998, Blood

Yaccoby S. et al, 2004, Leukemia

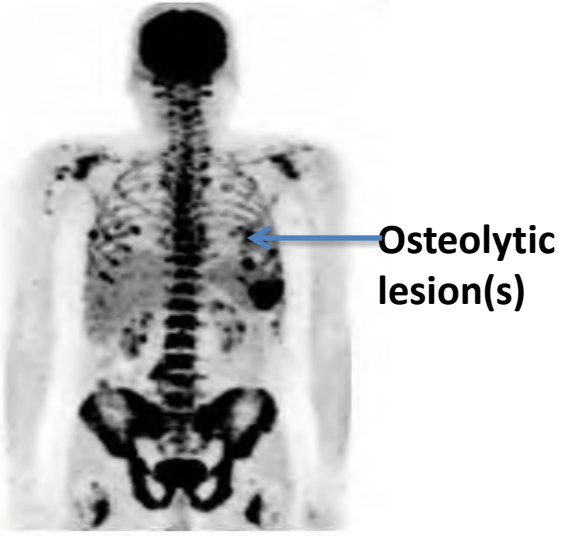
Multiple Myeloma: cancer of plasma cells

- Multiple myeloma (MM) is a type of plasma cell malignancy, currently incurable
- Clinical course characterized by remissions & relapses
- Patient survival has improved [3 year OS 42% past Vs. 80% current] in recent years
- Estimate ~20,000 new cases, 10,000 deaths in the US/ year

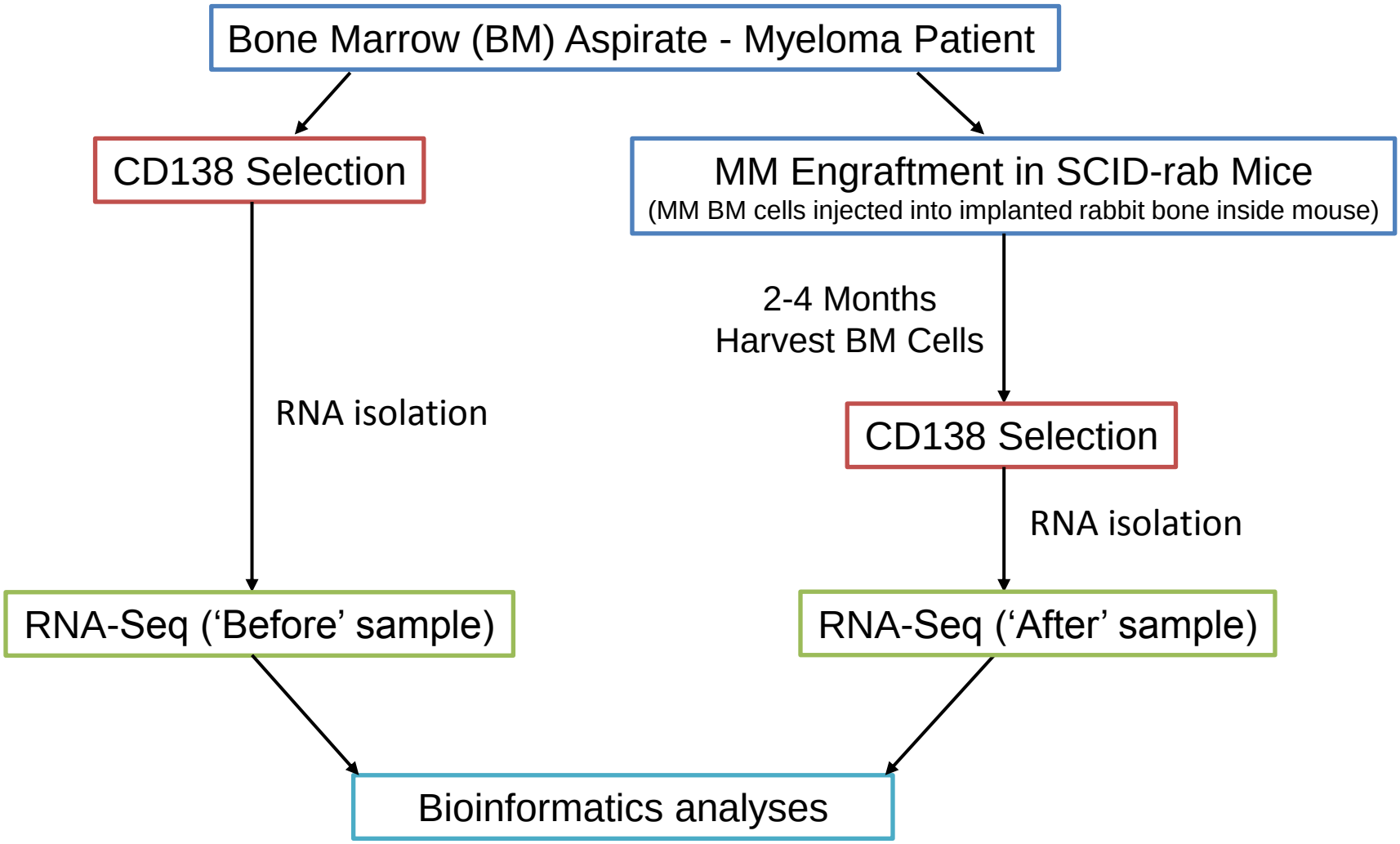
Bone marrow aspirate → abundant plasma cells



PET Scan showing diffuse and focal lesions

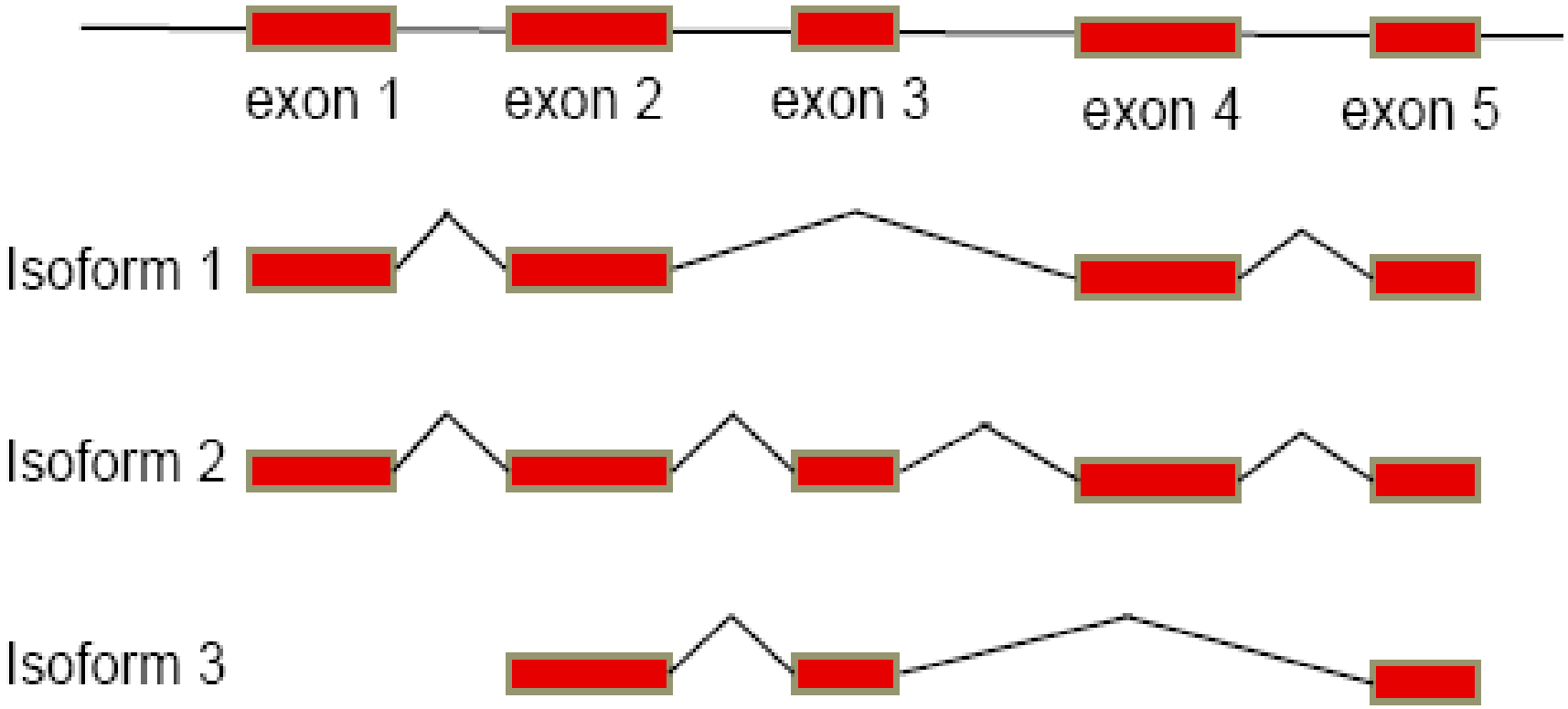


Experimental design

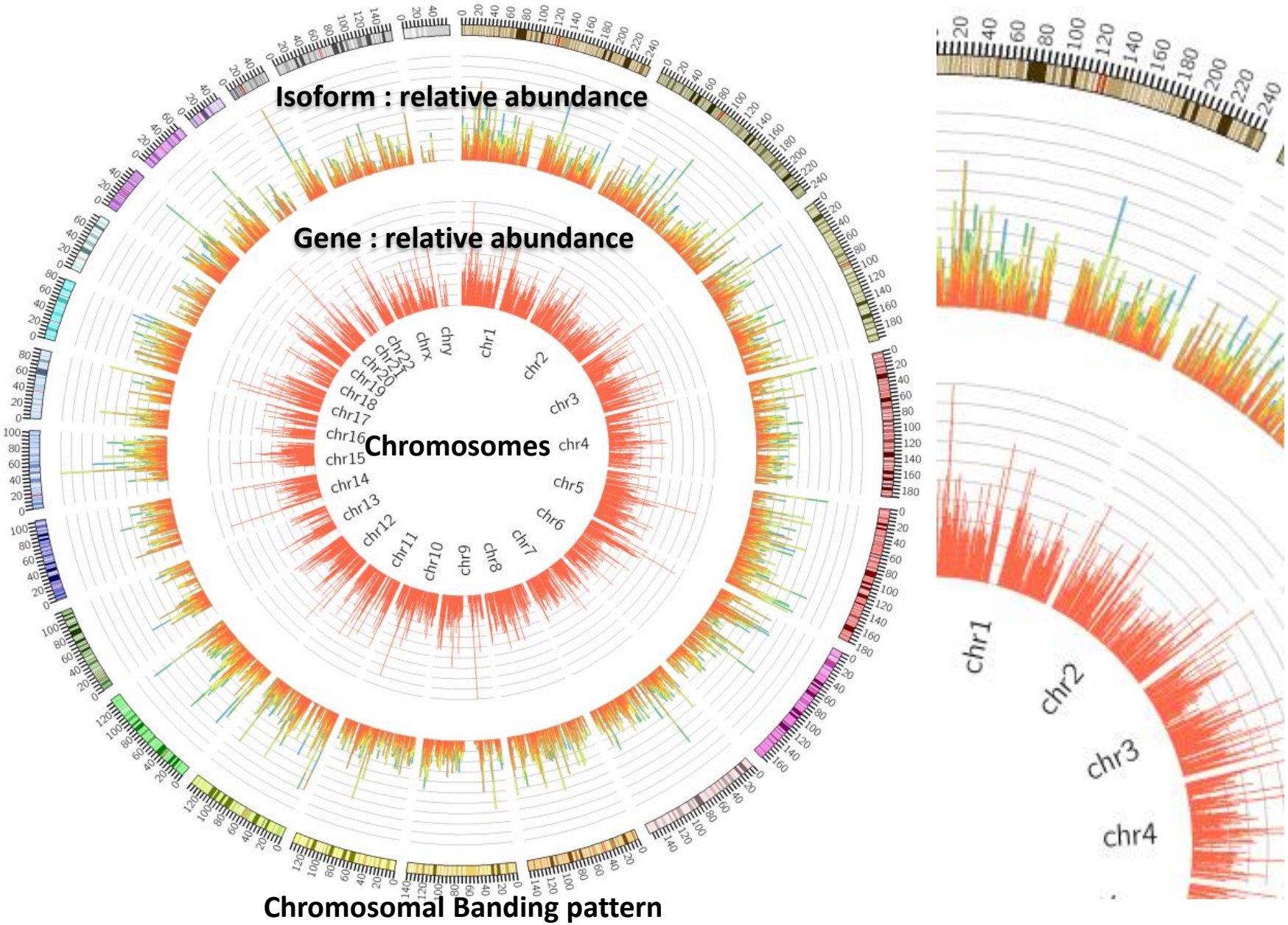


RNA-Seq data

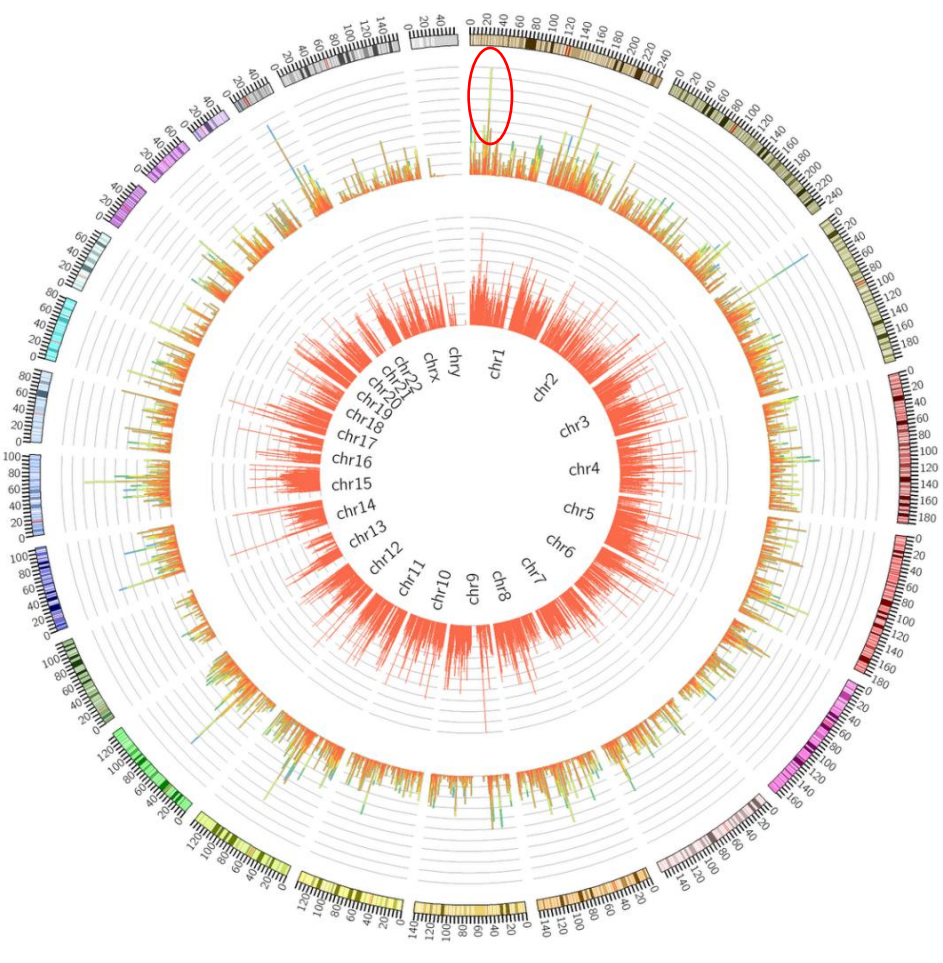
Isoform – mRNAs derived from the same locus , different combination of exons



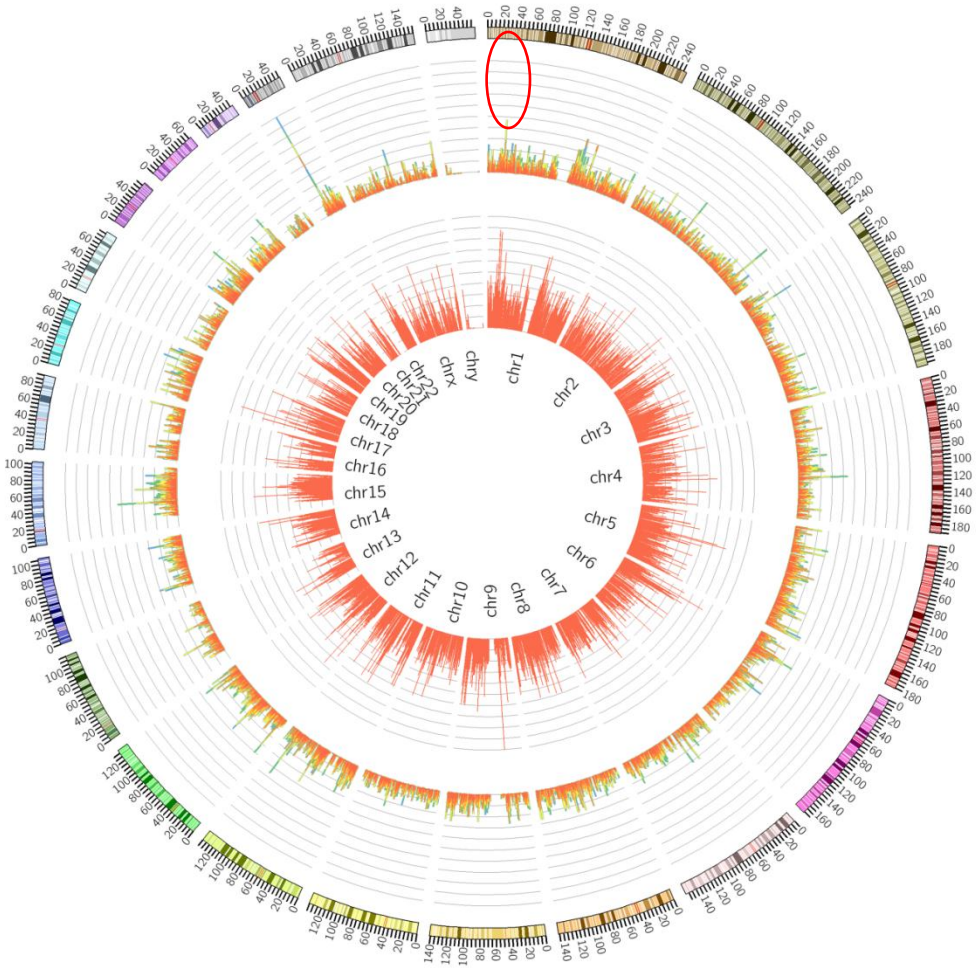
Ways to visualize complex NGS data



Visualizing RNA-seq “Before” & “After” an Experimental Condition (Engraftment)

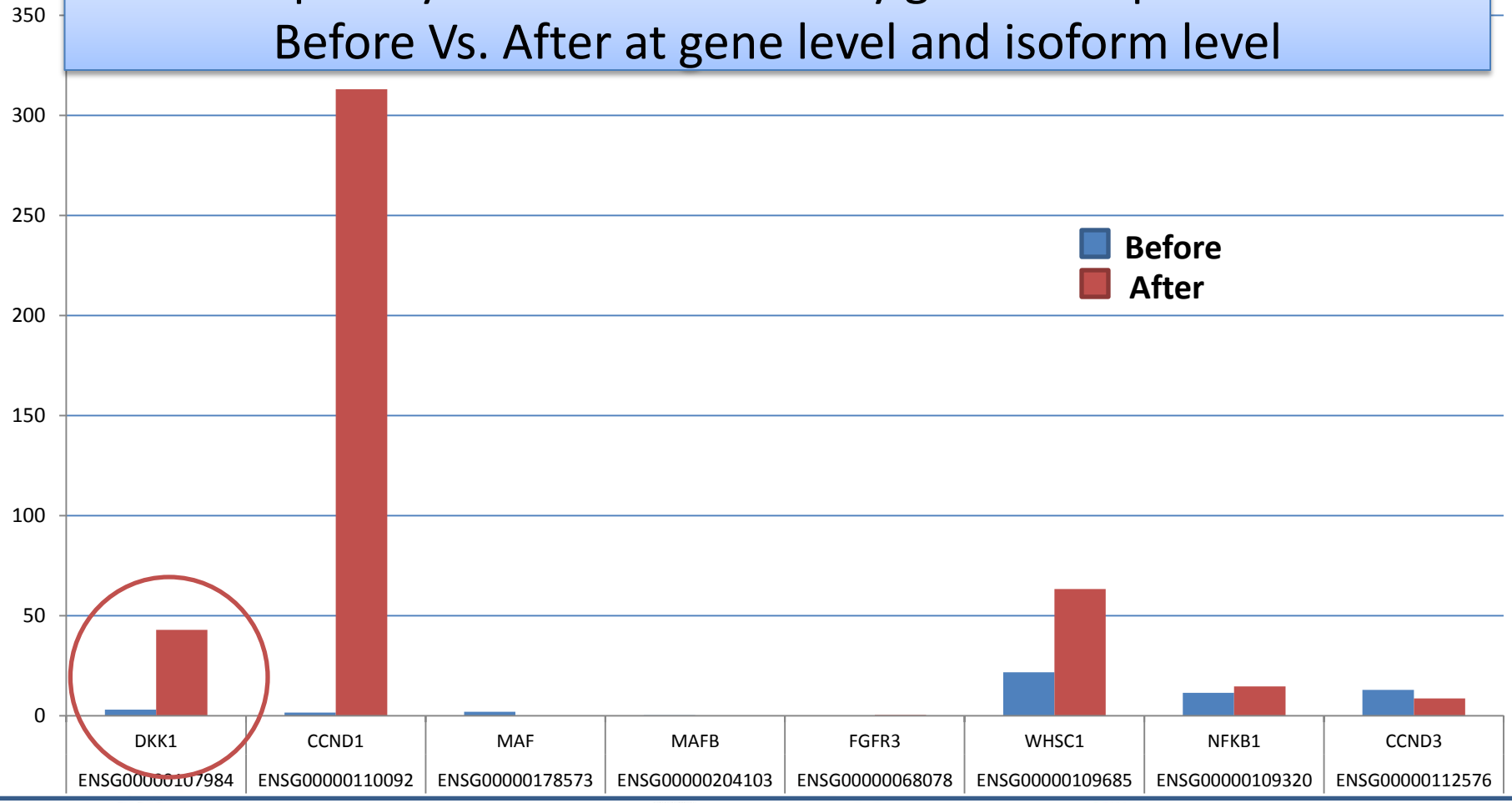


Before

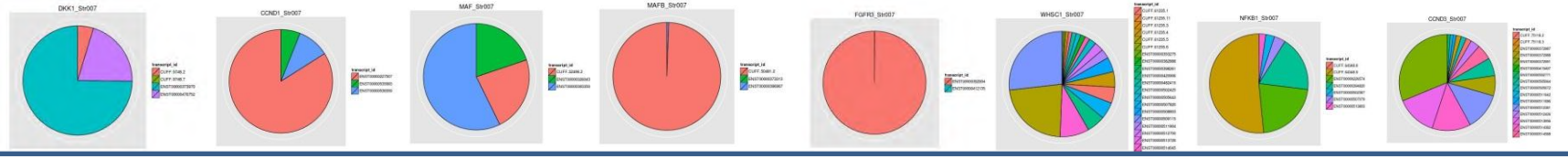


After

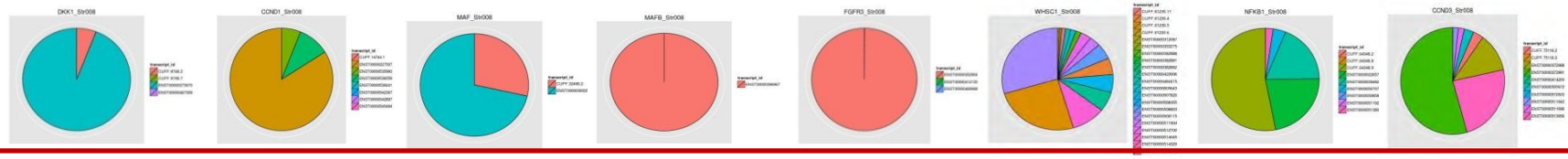
Multiple Myeloma 8 selected key genes – expression in Before Vs. After at gene level and isoform level



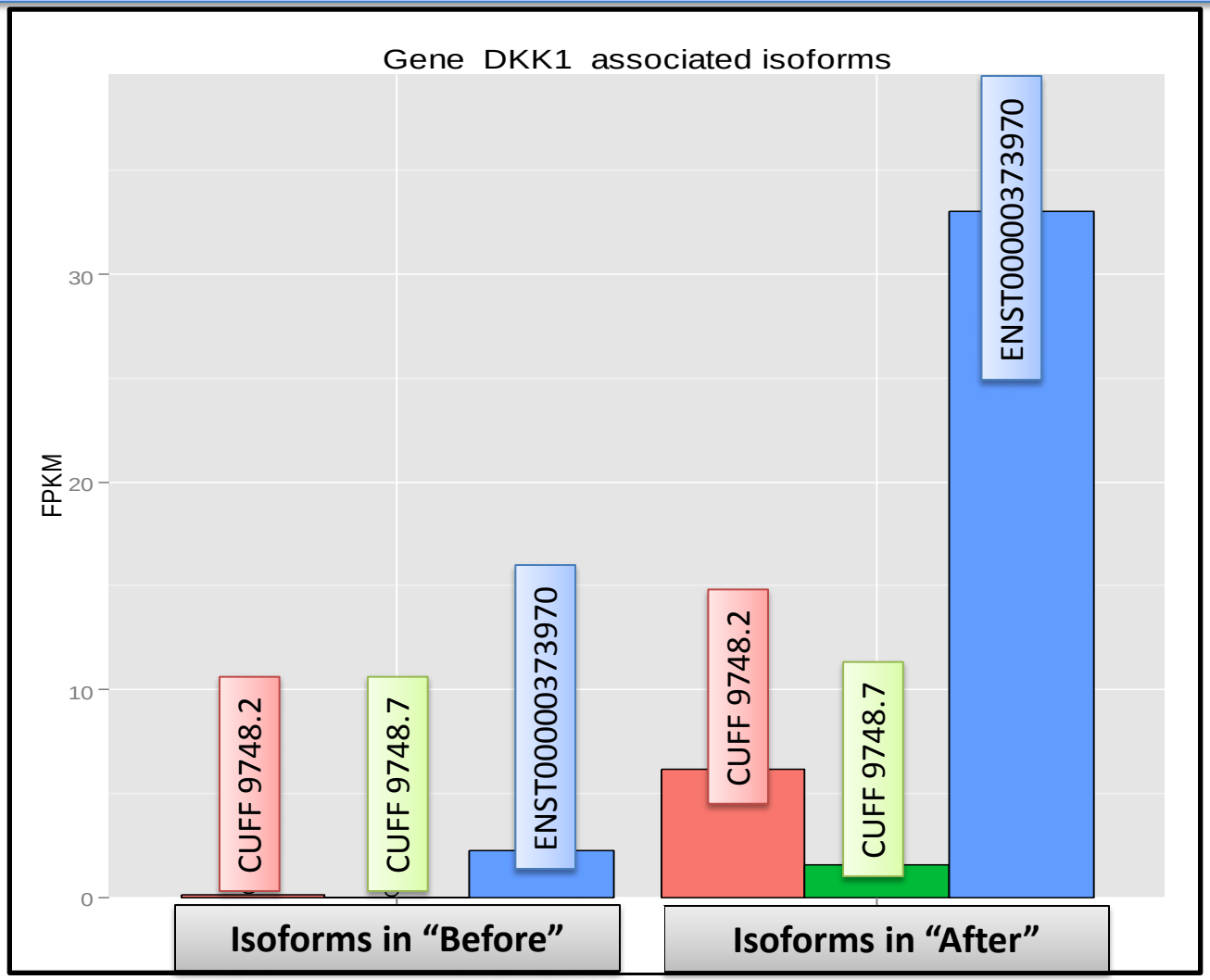
Before

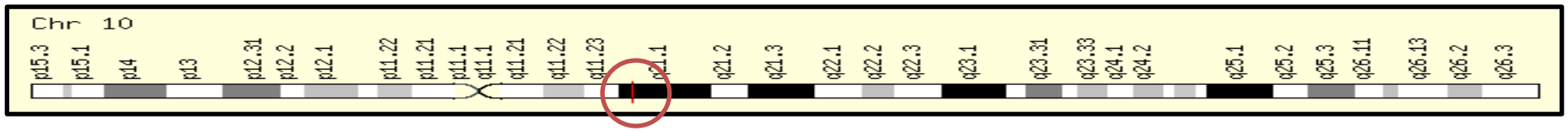


After

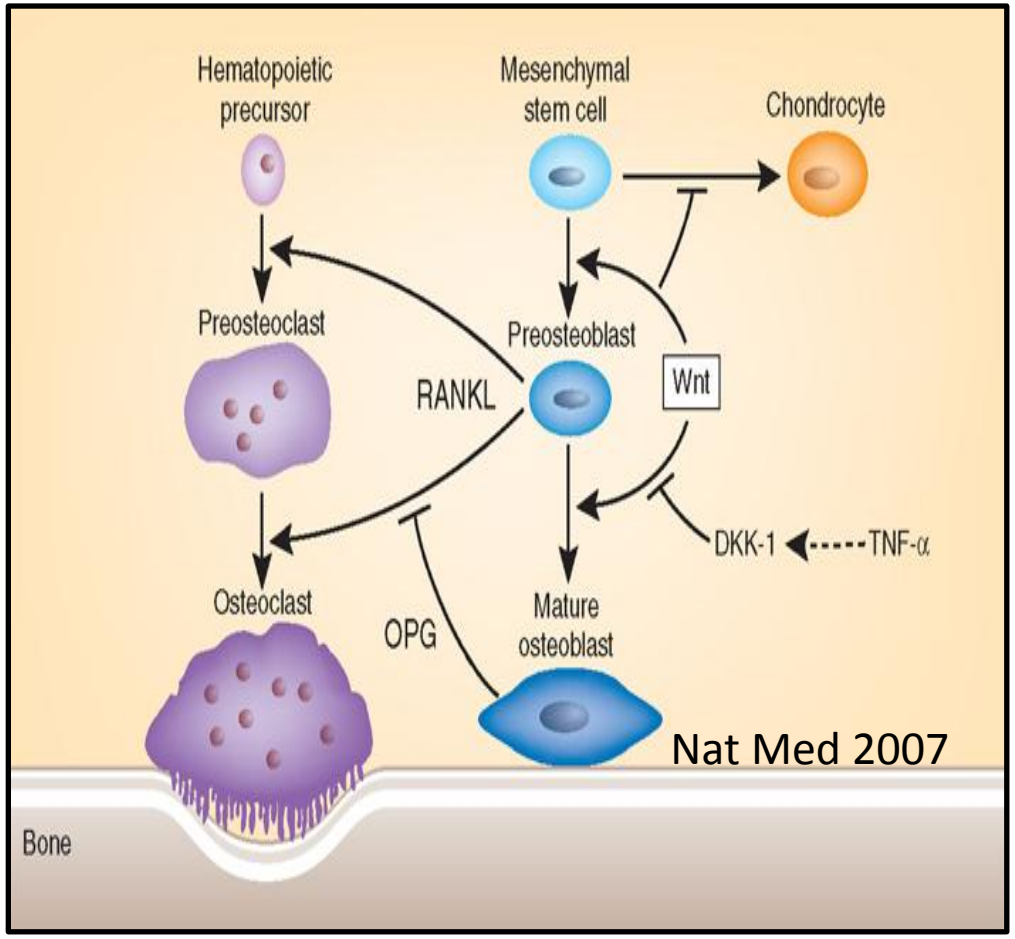


Zeroing in on key findings (*DKK1*)





RNA-Seq characterization of Multiple Myeloma functionally relevant gene : DKK1



- MM cells → Δbone micro-environment
- Wnt signaling essential → bone homeostasis
- DKK1 antagoizes Wnt signalling
- Osteoblast proliferation ↓
- Osteoclast activity ↑ → Bone resorption as seen in MM mice models

Summary

- Animal models : critical significance in research
- RNA-seq is discovery based, facilitates discovery of new genes/isoforms
- Illustration of a novel mouse model (SCID-rab) for MM engraftment using RNA-Seq : Before – After study with actual patient sample
- This experiment found “up regulated” DKK1 isoforms
- Animal model + RNA-Seq technology = may accelerate bench to beside discoveries

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