Priorities of the KIDNEY/BLADDER CANCERS Progress Review Group

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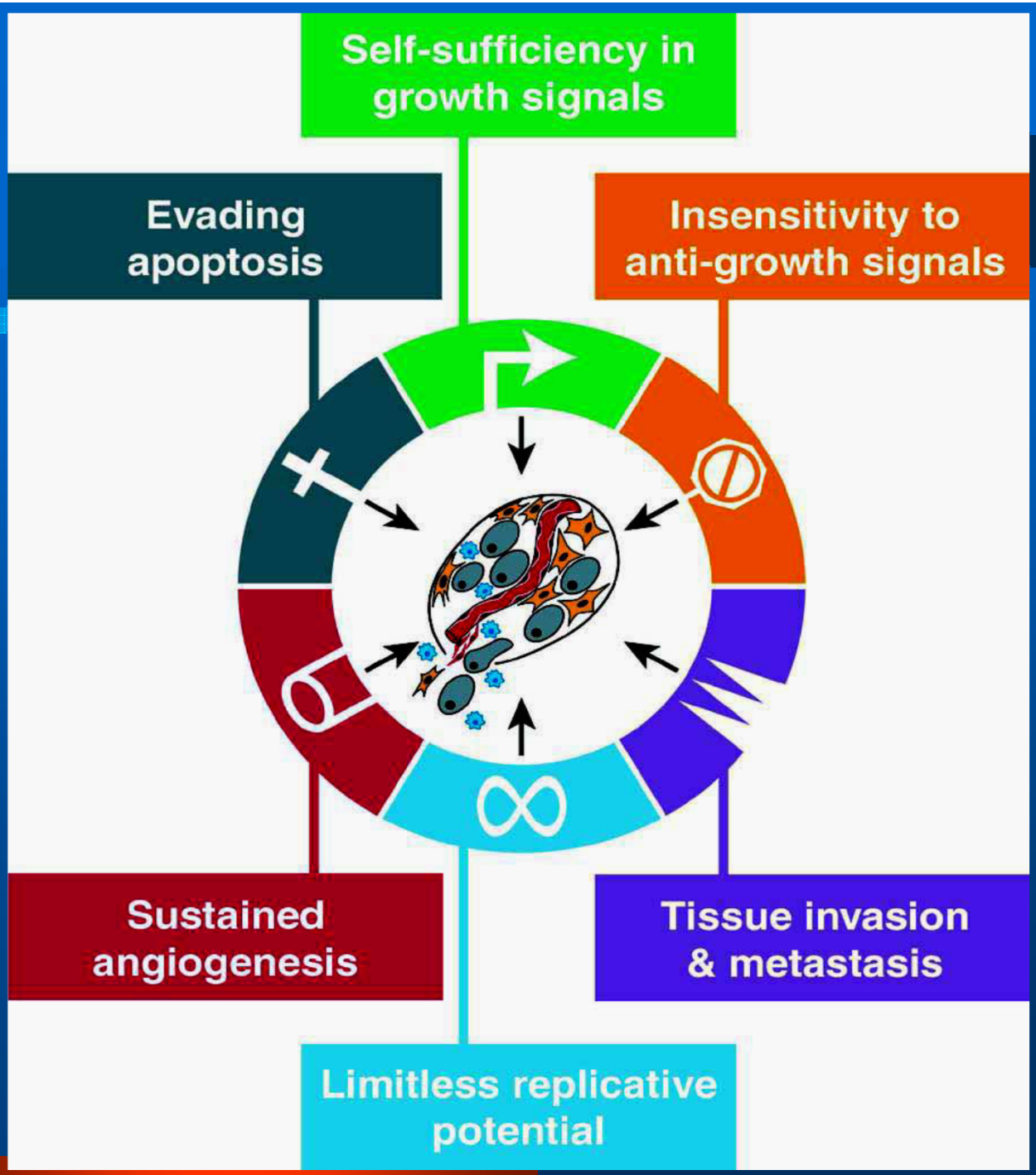
Genitourinary Malignancies, US 2000

Organ Site	Cases/Year*	Deaths/Year*
Prostate	180,400	31,900
Kidney	31,200	11,900
Bladder	53,200	12,200
Testis	6,900	800
	270,000	57,000
Total cancers	1,268,000 (21%)	553,400(10%)



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Kidney Cancer

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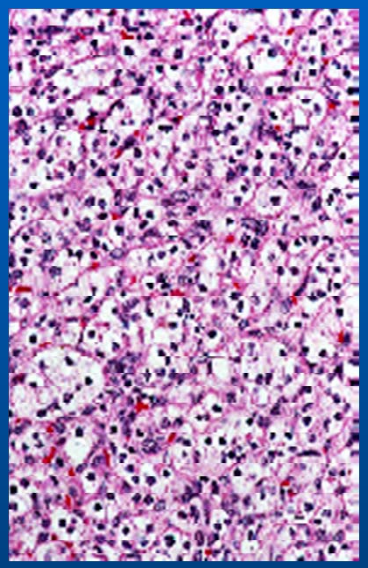
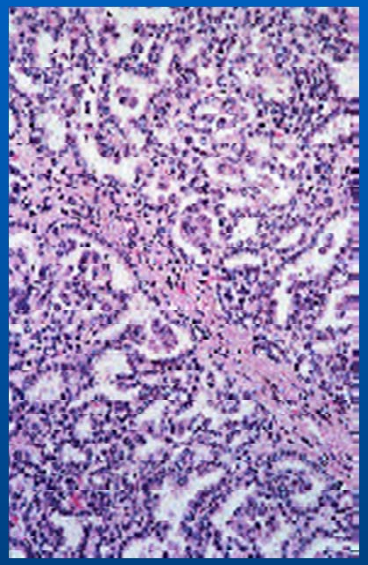
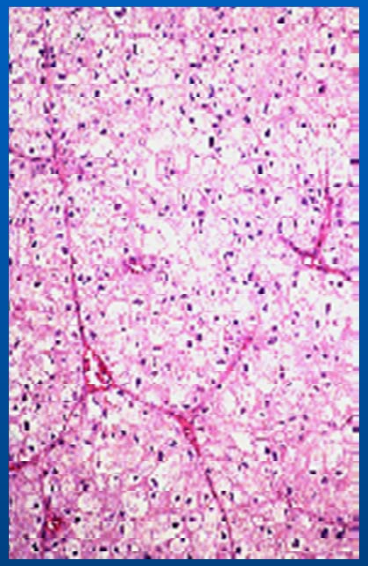
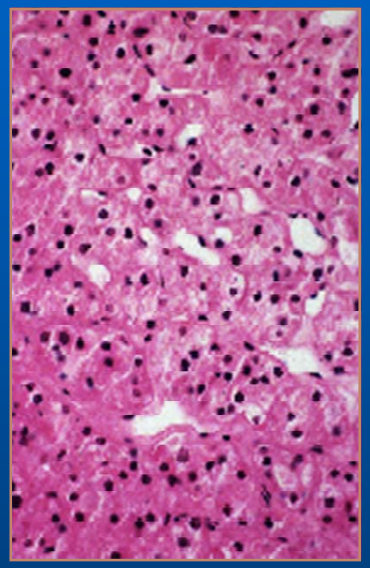
Human Renal Epithelial Neoplasms

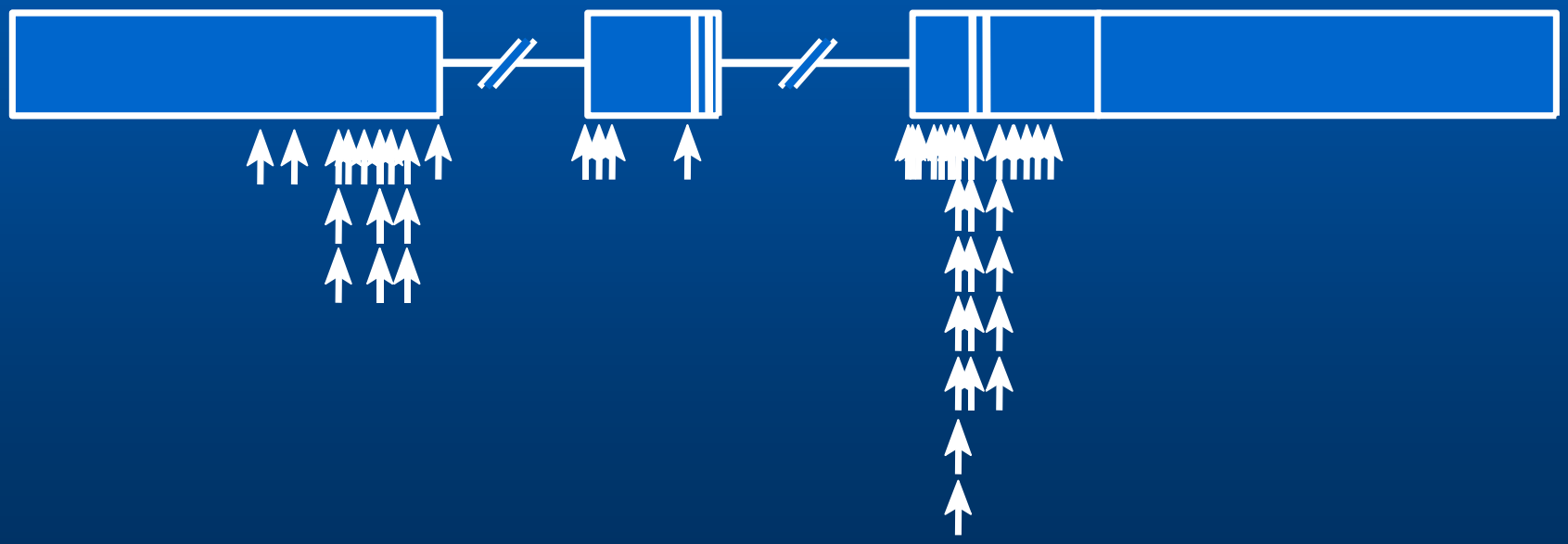





Type:	Clear cell	Papillary	Chromophobe	Oncocytoma
Freq (%):	75	15	5	5

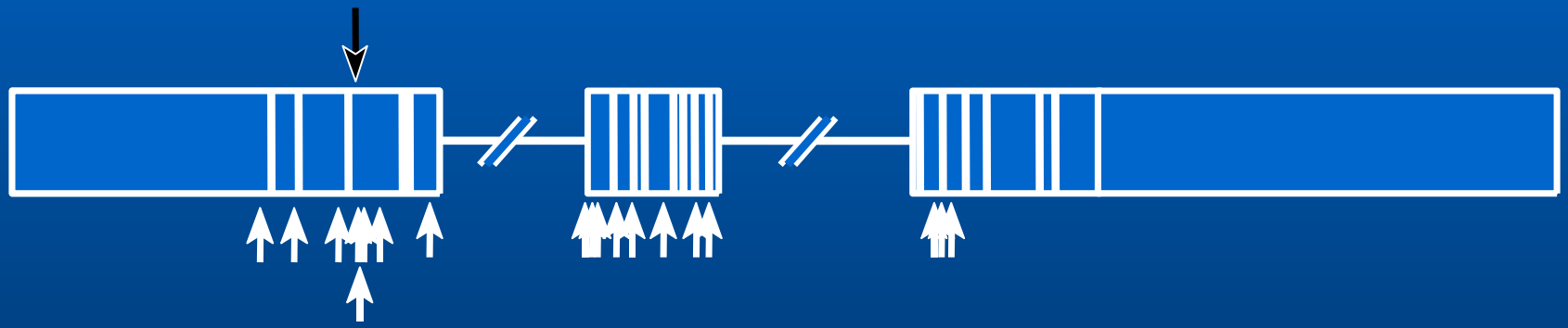
Renal Carcinoma: Genes

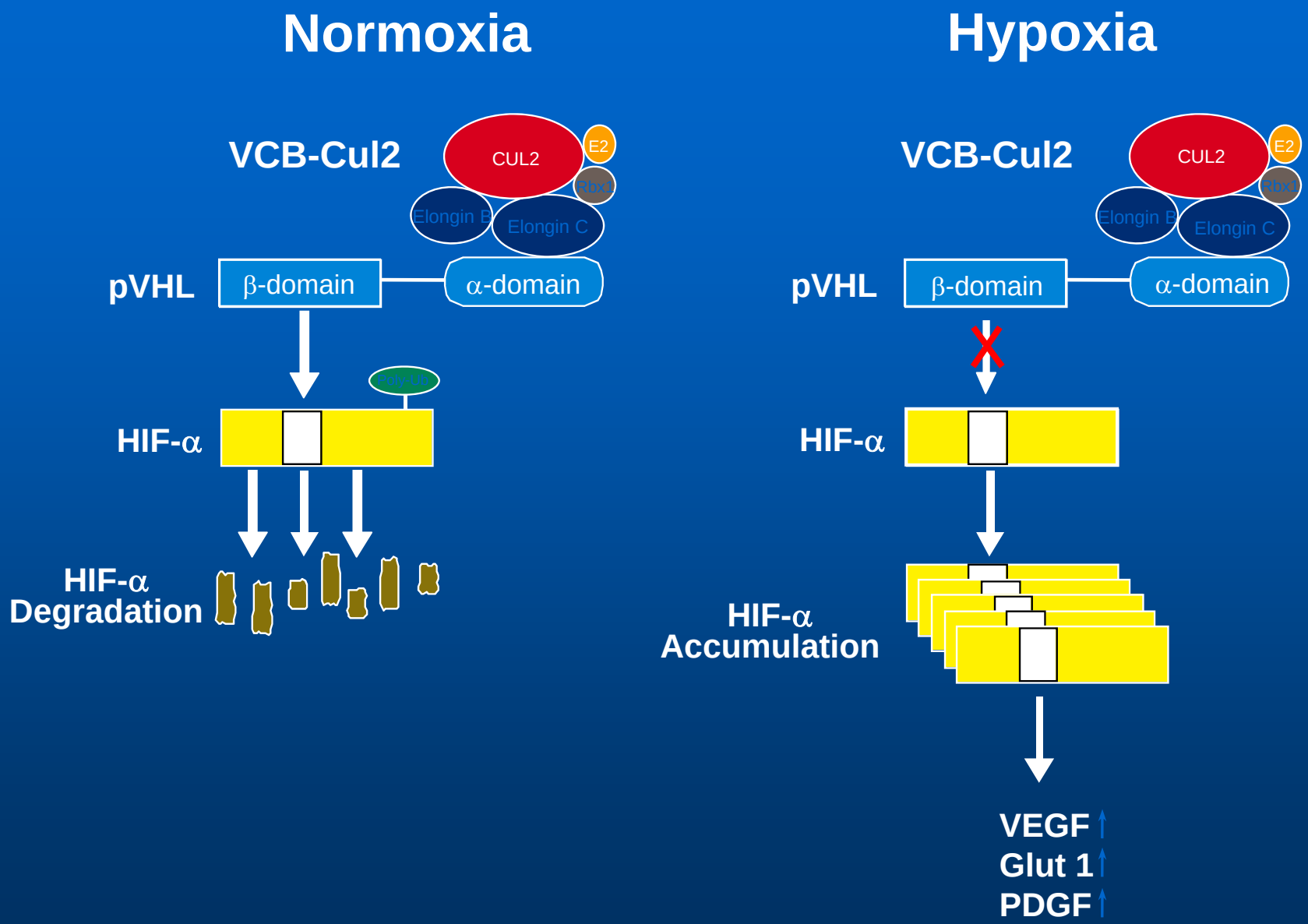
Gene Histology	Hereditary Form	RCC
1. VHL Gene RCC (Chr 3)	von Hippel Lindau (VHL)	Clear Cell
2. Met Gene (Chr 7)	Hereditary Papillary Renal Carcinoma (HPRC)	Papillary RCC (Type 1)
3. BHD 1 (Chr 17)	Birt Hogg Dube (BHD)	Chromopobe RCC Oncocytoma “Transition” RCC
4. LRCC (Chr 1)	Leiomatomosis RCC (LRCC)	Papillary (Type 2)

Germline VHL Mutations

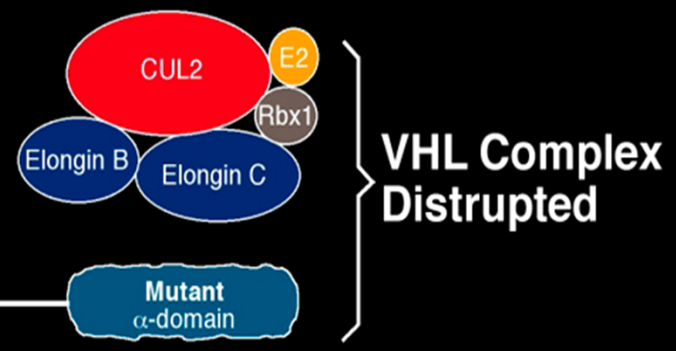


Sporadic Clear Cell RCC VHL Gene Mutations

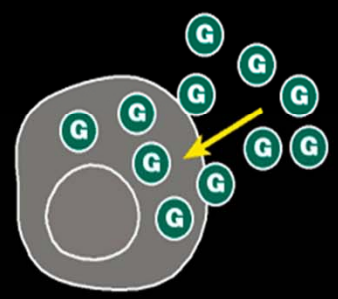



Normoxia
VCB-Cul2
CUL2
E2
Rbx1
Elongin B
Elongin C
pVHL
β-domain
α-domain
Poly-Ub
HIF-α
HIF-α
Degradation
Hypoxia
VCB-Cul2
CUL2
E2
Rbx1
Elongin B
Elongin C
pVHL
β-domain
α-domain
HIF-α
HIF-α
Accumulation
VEGF
Glut 1
PDGF

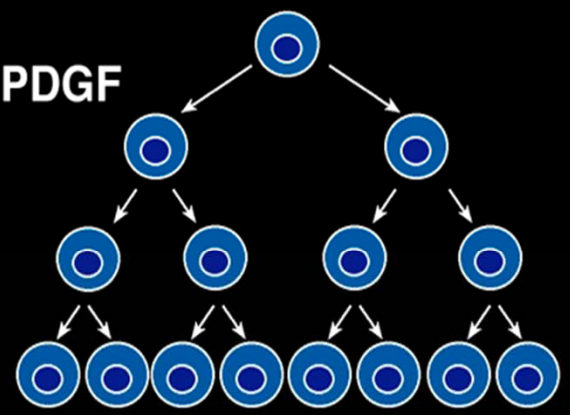
VHL Gene Mutation (RCC)



Angiogenesis



Glucose Transport



Autocrine Growth Stimulation

Bladder Cancers

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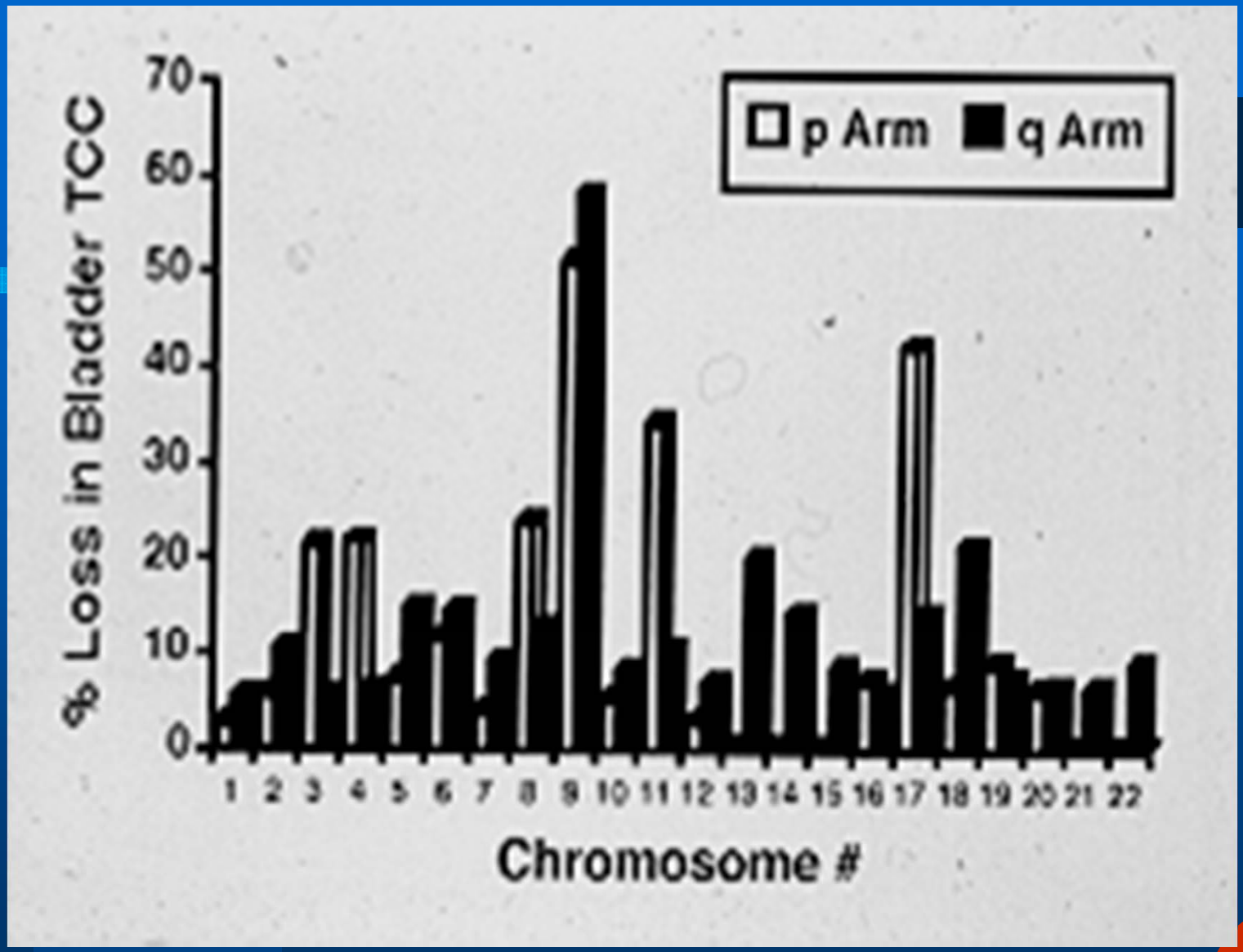

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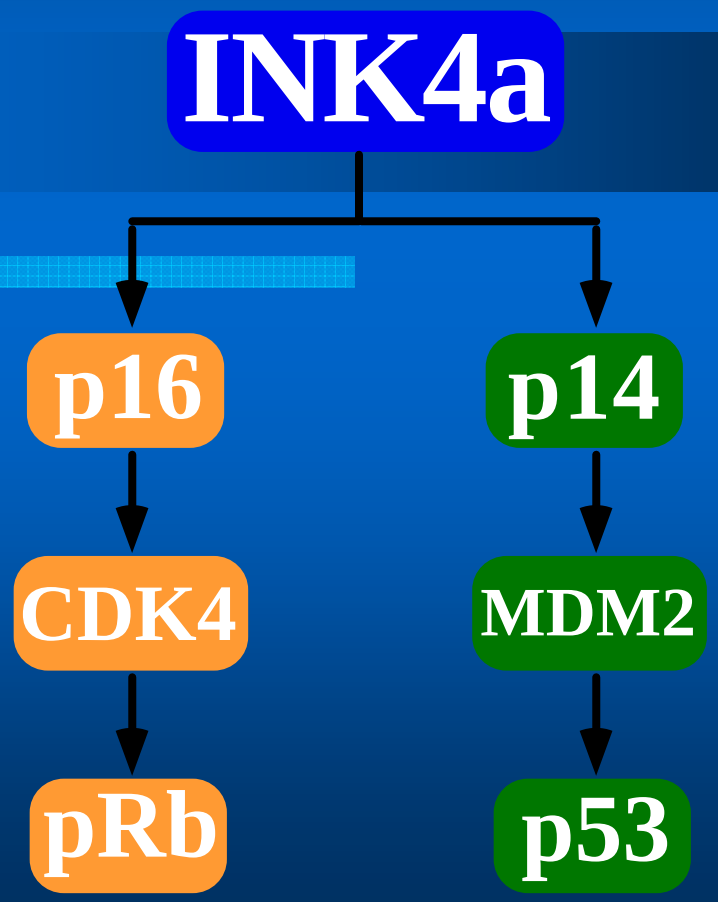
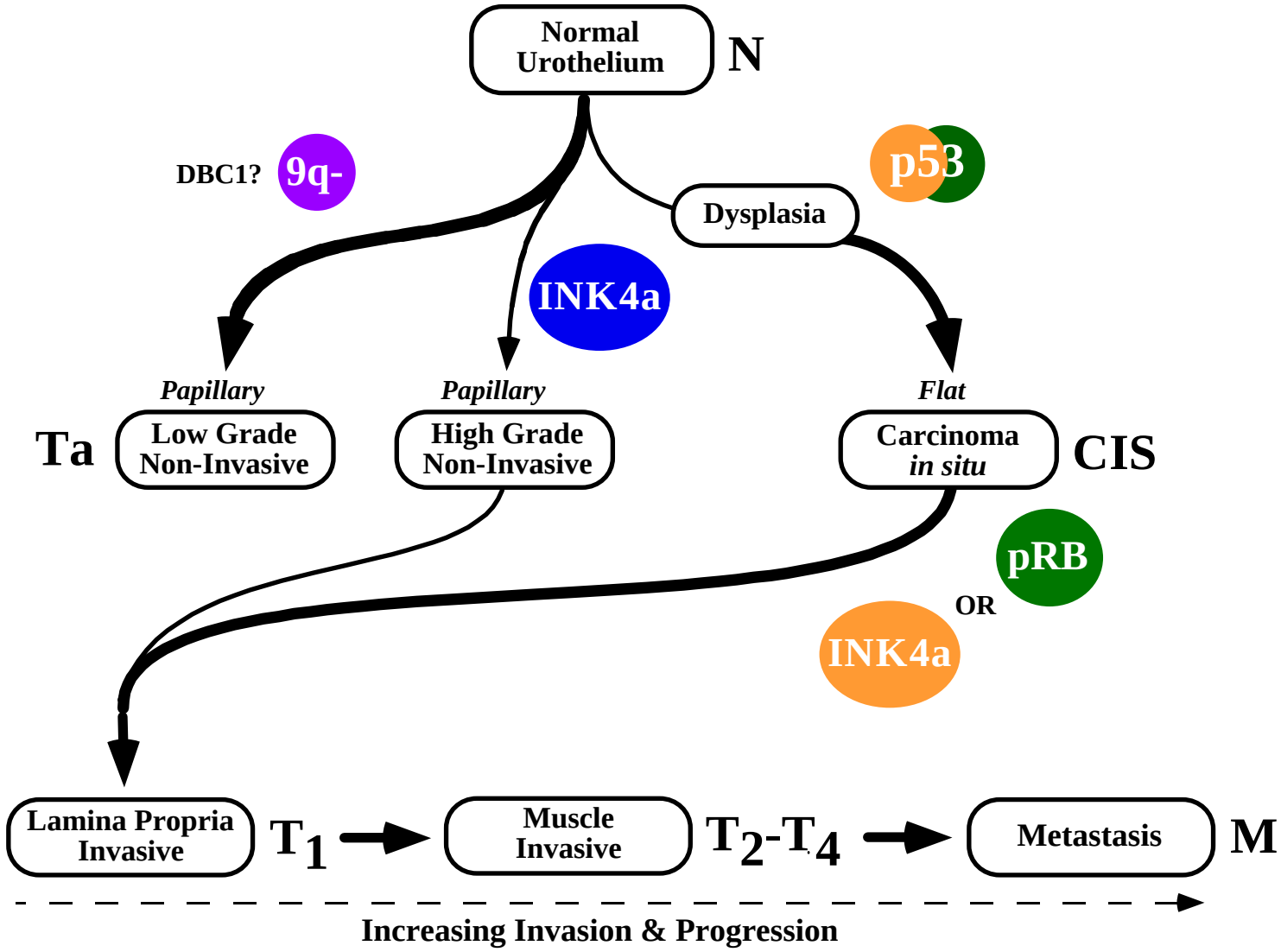
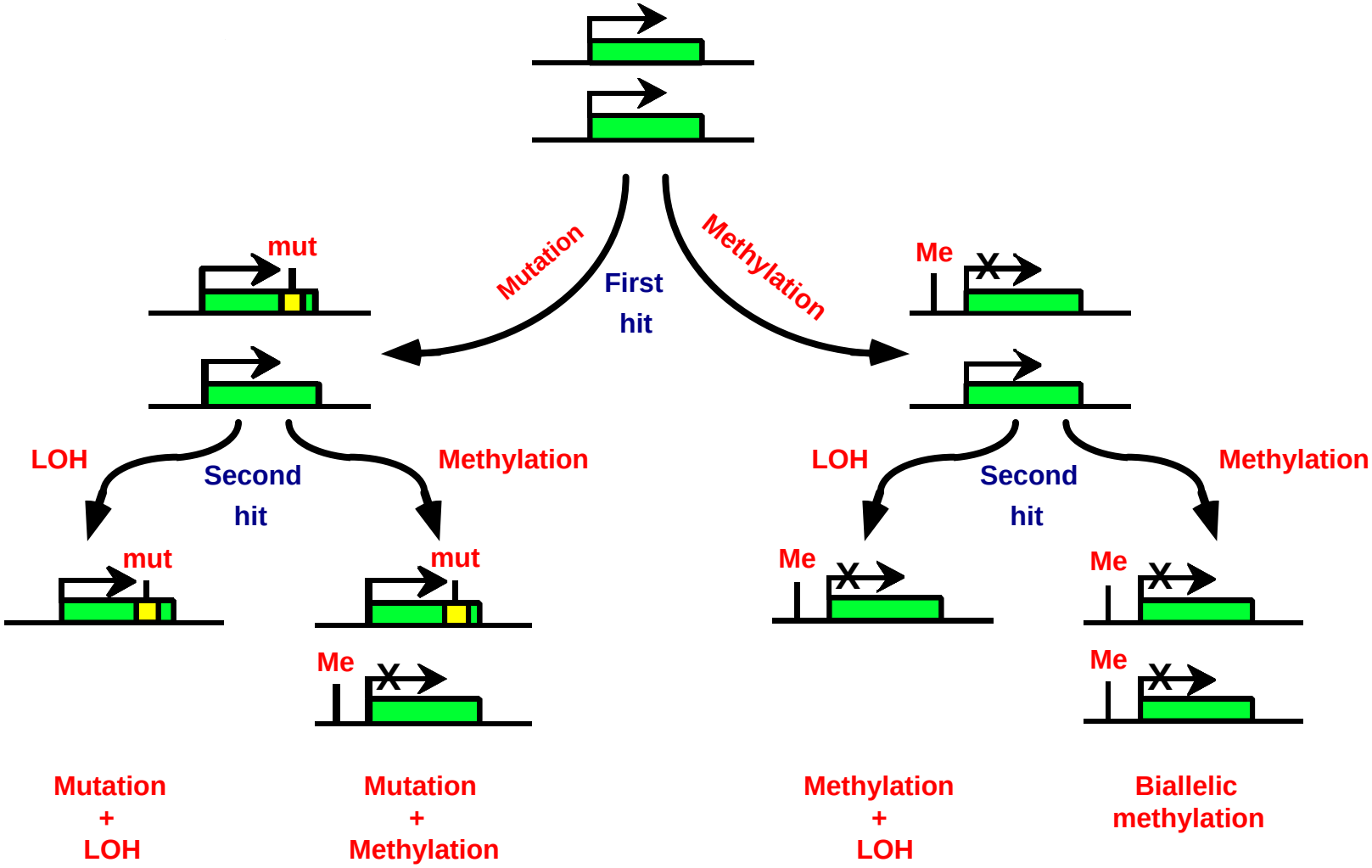
DUAL PATHWAY MODEL FOR BLADDER CARCINOGENESIS



Model for Bladder Cancer Progression




Mutation
First
hit
Methylation
mut
Me
LOH
Second
hit
Methylation
LOH
Second
hit
Methylation
mut
mut
Me
Me
Me
Me
Mutation
+
LOH
Mutation
+
Methylation
Methylation
+
LOH
Biallelic
methylation

What's Needed?

- All pathways in each tumor
- Mode of inactivation
- Longitudinal studies
- Better animal models
- Tailored therapy
- Earlier detection

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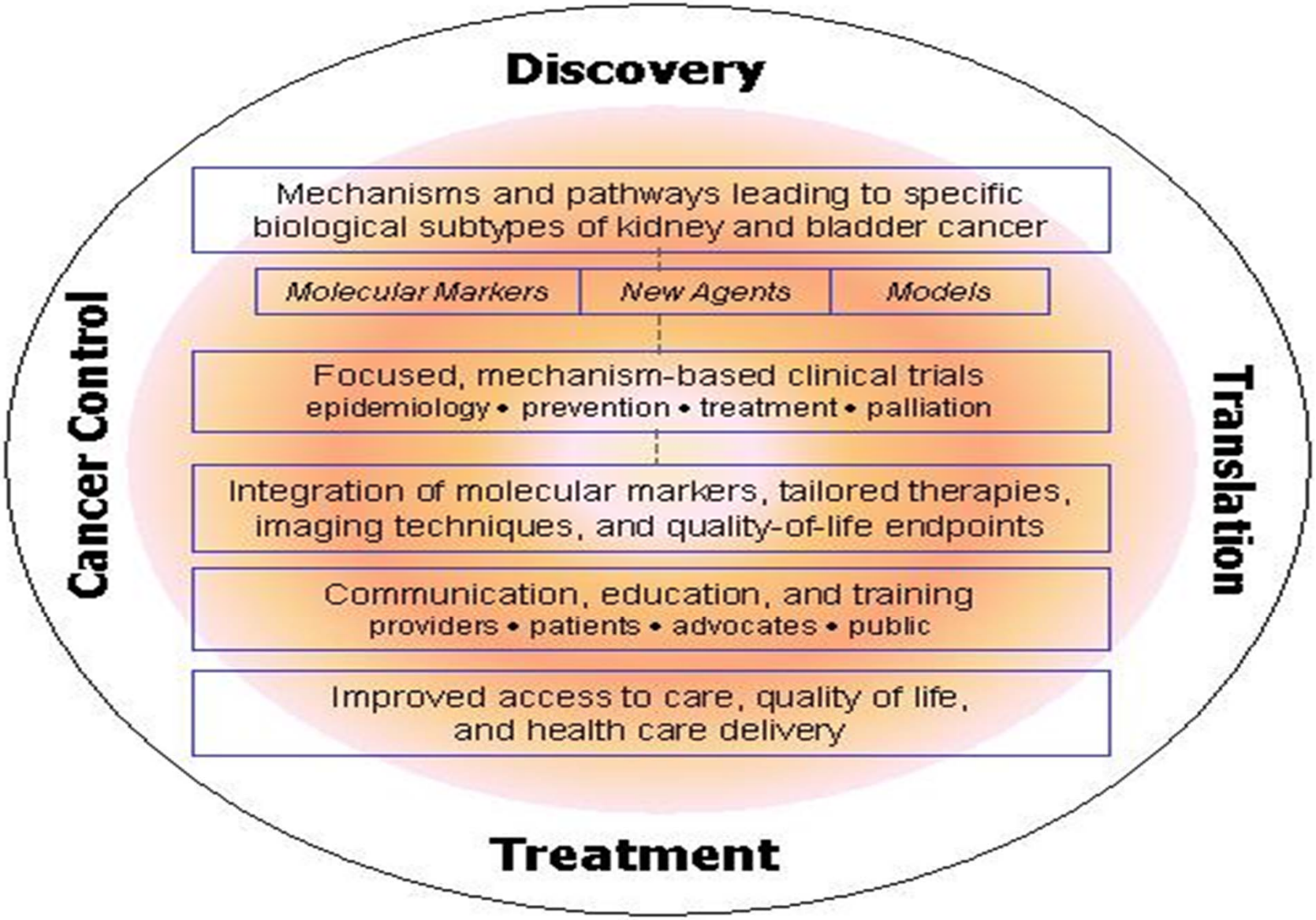

Discovery-1

Understand the biological mechanisms underlying the risk factors for kidney and bladder cancer phenotypes.

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Discovery-2

Identify global genetic, epigenetic, RNA expression, and proteomic alterations in tumors and place them in specific biological pathways that are essential to development, progression, response to therapy, and maintenance of subtypes of bladder and kidney cancers.

Discovery-3

Understand the role of stroma and intercellular signaling in organogenesis, tumor development, and maintenance of malignant phenotypes in bladder and kidney cancers.

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Discovery-4

Generate and characterize transgenic models, including conditional knock-out and knock-in strategies and orthotopic models, of bladder and kidney cancers, focusing on the use of tissue-specific promoters and targeting human disease-related genetic events. These models will allow identification and validation of prognostic, preventive, and therapeutic targets and their inhibiting agents.

Translation-5

Examine blood, urine, premalignant, and tumor tissue before prevention and therapy trials to identify and quantify disease and identify targets for therapy and predictors and mechanisms of response, resistance, progression, and relapse.

Translation-6

Facilitate the development and utilization of noninvasive or minimally invasive techniques to image and assess the biological and clinical effects of targeted therapeutics.

Translation-7

Identify and prioritize agents—alone or in combination—that target known cancer growth and progression pathways.

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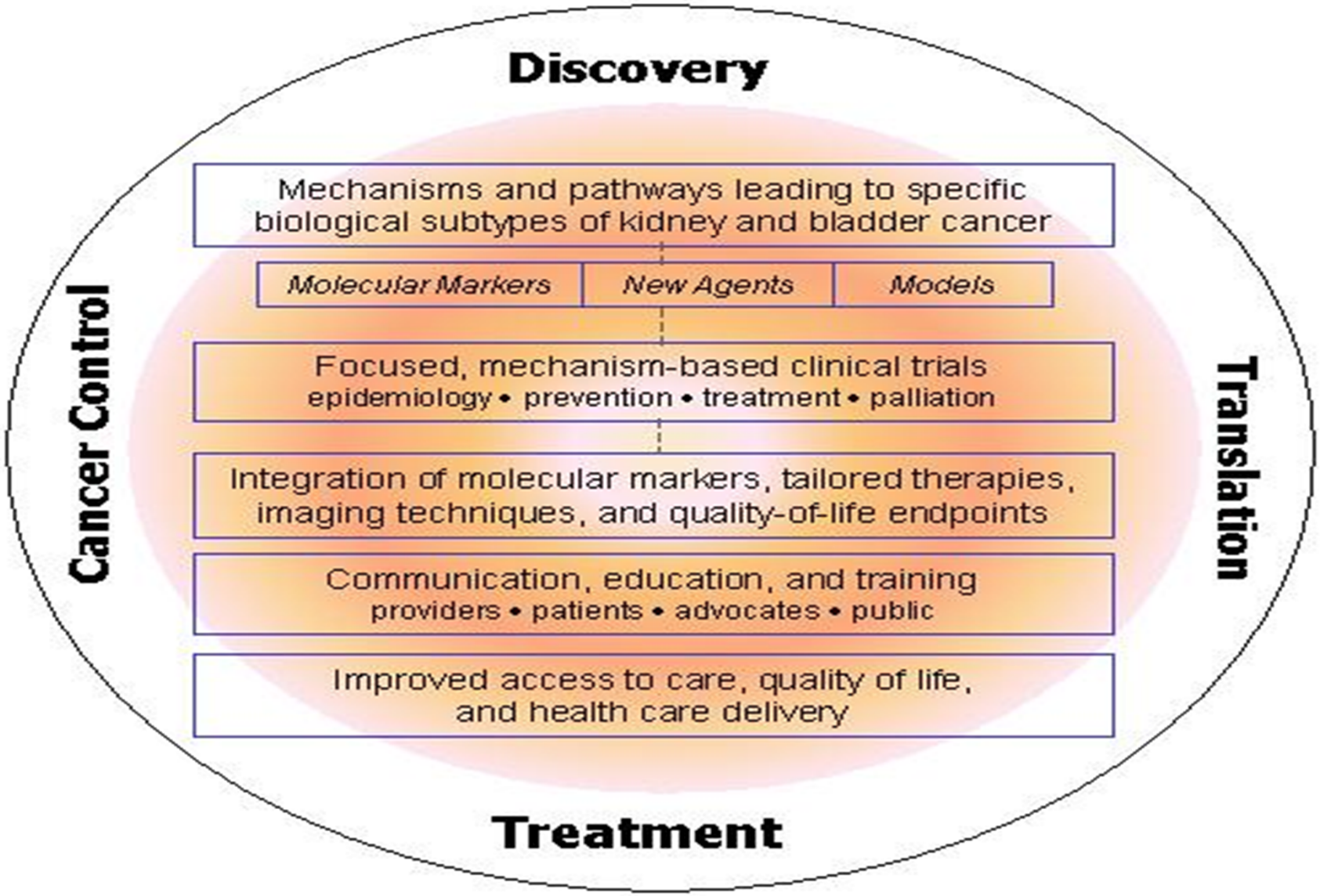
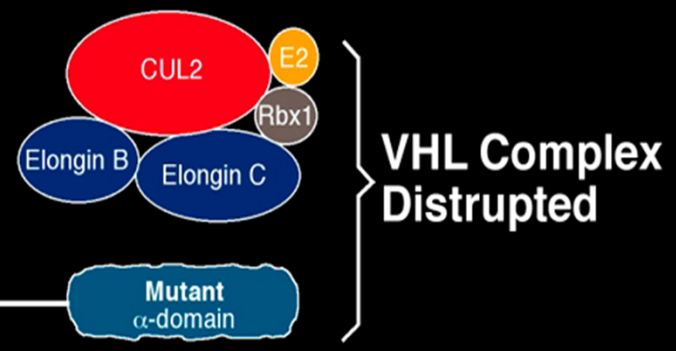


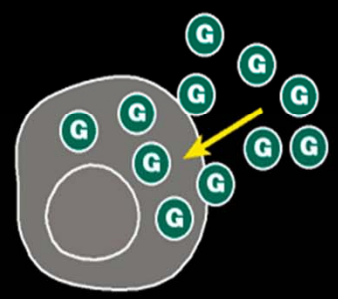
Treatment-8

Develop innovative therapeutic strategies that will eradicate disease, preserve organ function, and maintain quality of life, using mechanism-based agents that take into account known prognostic variables, molecular characteristics of tumors, assays of targeted effects, surrogate markers of efficacy, and novel delivery strategies.

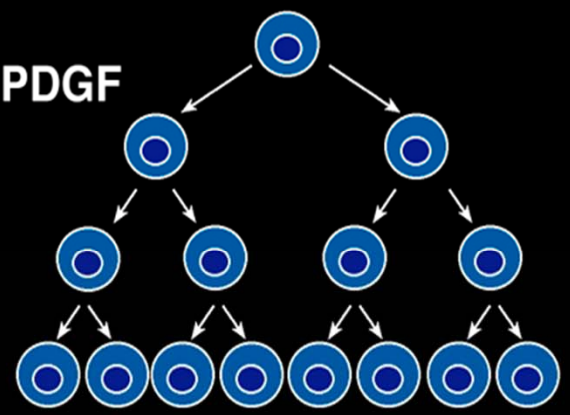
VHL Gene Mutation (RCC)



Angiogenesis



Glucose Transport



Autocrine Growth Stimulation

Major Responses to anti-VEGF

	N=	CR	PR	RR
Placebo	40	0	0	0%
High-Dose Ab	39	0	4*	10%
Low-Dose Ab	37	0	0	0%

*Durations 44+, 15, 9, 6 months/ Yang et al 2002

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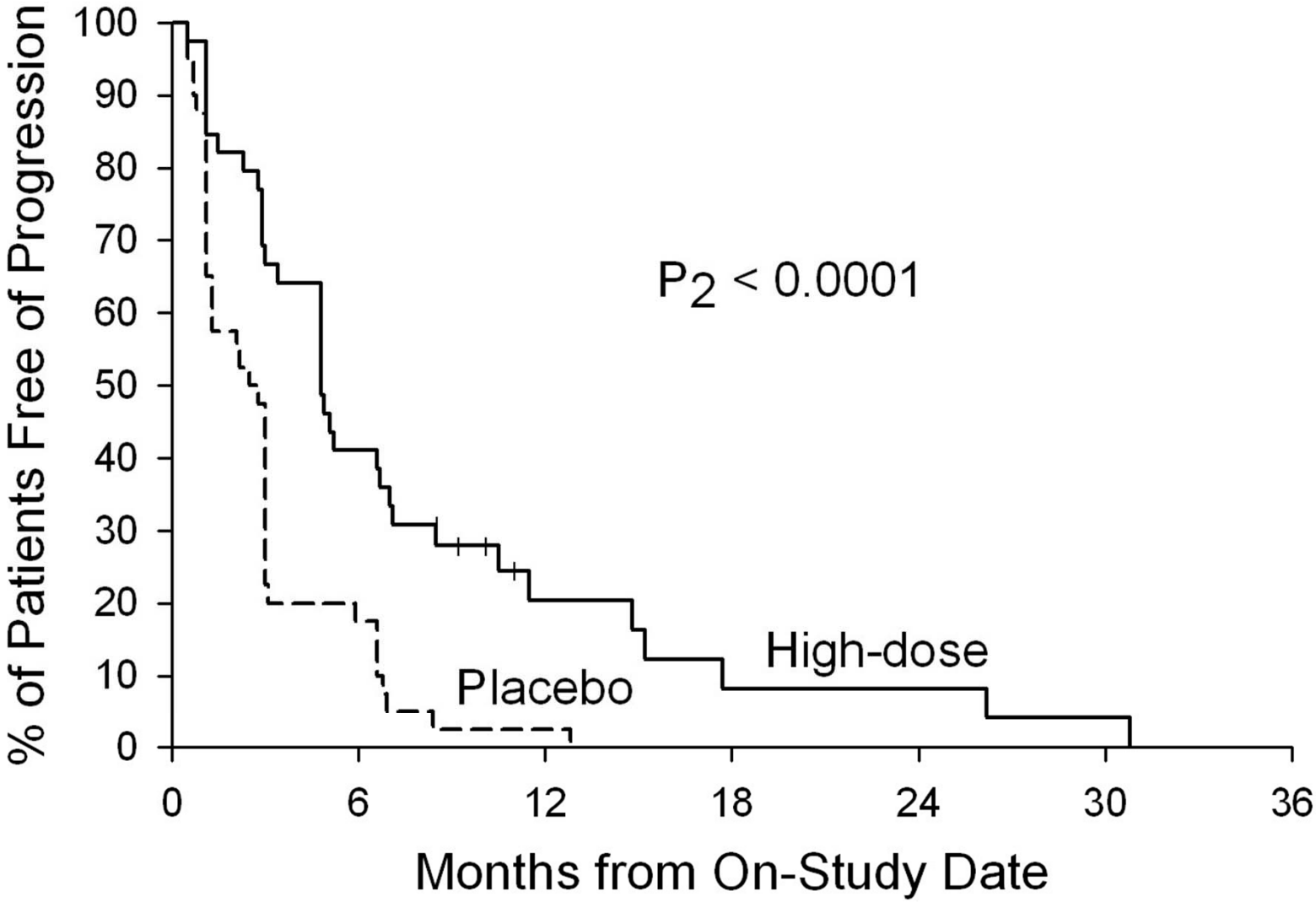
Time to Progression
High-Dose Anti-VEGF vs. Placebo



Treatment-9

Develop and improve approaches to risk assessment of localized and advanced disease—which take into account known prognostic variables, including stage, histology, and novel molecular factors—to direct therapy.

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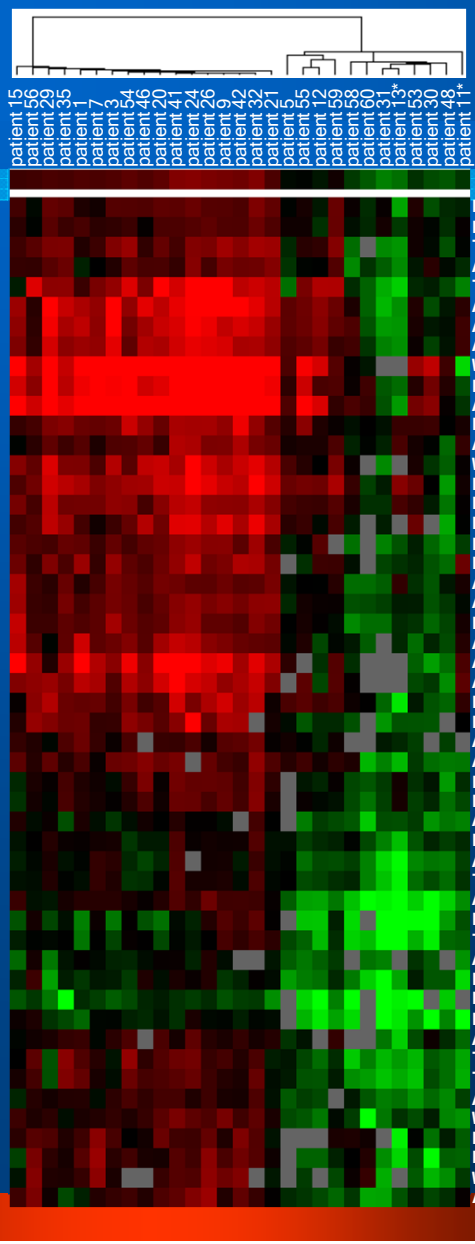
patient 46
patient 54
patient 35
H36032 clear
H36019 clear
patient 7
patient 21
patient 3
patient 15
patient 20
patient 1
patient 24
No 33
No 67
No 47
patient 41
patient 26
patient 42
patient 32
patient 29
patient 8
patient 9
patient 23
UC sRCC1
patient 34
steNo23chromo
patient 14
H36020 clear
UCK7 onco
BHD 1
UCK6 chromo
H36034 chromophobe
H36036 chromophobe_sarcomatoid
H36022 chromophobe_
No 28
GR No4
UC pRCC1
patient 48
patient 56
patient 19
H36024 papillary
H36021 papillary
H36023 papillary_pelvic
H36018 papillary
UCK3 CCRCC
No 38
H36035 clear_sarcomatoid
steNo21sRCC_
H36033 sarcomatoid
patient 13
patient 11
patient 31
No 72
No 66
No 64
patient 58
UCK12 P1
UCK12 M1
patient 51
patient 60
patient 55
patient 5
patient 12

Prognostic set of genes



N35086 FYN oncogene related to SRC, FGR, YES
N66144 FYN oncogene related to SRC, FGR, YES
T47312 insulin receptor
AA001614 insulin receptor
T80232 phosphodiesterase I/nucleotide pyrophosphatase 2 (autotaxin)
AA490694 hevin
AA159194 FAT tumor suppressor (Drosophila) homolog
AA486082 serum/glucocorticoid regulated kinase
W60845 cell division cycle 42 (GTP-binding protein, 25kD)
N34362 regulator of G-protein signalling 5
AA668470 regulator of G-protein signalling 5
H84815 Rab9 effector p40
AA669136 transcription factor 4
W72803 ESTs, Weakly similar to KIAA0768 protein [H.sapiens]
R22412 platelet/endothelial cell adhesion molecule (CD31 antigen)
R56211 platelet-derived growth factor receptor, beta polypeptide
N39240 ESTs
H74106 LIM binding domain 2
H72113 CD34 antigen
AA777910 Homo sapiens clone 23698 mRNA sequence
AA680300 Homo sapiens clone 23698 mRNA sequence
R32440 Homo sapiens clone 23698 mRNA sequence
AA173109 ESTs
AA432292 ESTs,
AA055440 sprouty (Drosophila) homolog 1 (antagonist of FGF signaling)
H68922 integrin, alpha 1
N29914 endothelin receptor type B
AA425382 ESTs
AA775447 alpha-2-macroglobulin
H99415 A kinase (PRKA) anchor protein 2
N51499 A kinase (PRKA) anchor protein 2
AA464644 LIM domain only 2 (rhombotin-like 1)
N74956 polymerase (RNA) II (DNA directed) polypeptide B (140kD)
AA704965 ESTs
T53298 insulin-like growth factor binding protein 7
AA099153 tissue inhibitor of metalloproteinase 3
N95226 KIAA0758 protein
T63971 KIAA0758 protein
AA189106 KIAA1102 protein
R23270 KIAA1102 protein
N36136 ESTs, Moderately similar to endomucin [M.musculus]
N93505 transmembrane 4 superfamily member 2
AA173408 ESTs
T71976 Phosphatidic acid phosphatase type 2b
T72119 Phosphatidic acid phosphatase type 2b
AA487034 transforming growth factor, beta receptor II (70-80kD)
W68396 KIAA0096 protein
N57594 Homo sapiens mRNA; cDNA DKFZp564E153 (from clone DKFZp564E153)
N94344 Homo sapiens mRNA; cDNA DKFZp564E153 (from clone DKFZp564E153)
W47641 Homo sapiens mRNA; cDNA DKFZp564E153 (from clone DKFZp564E153)
AA458653 Homo sapiens mRNA for GS3955, complete cds

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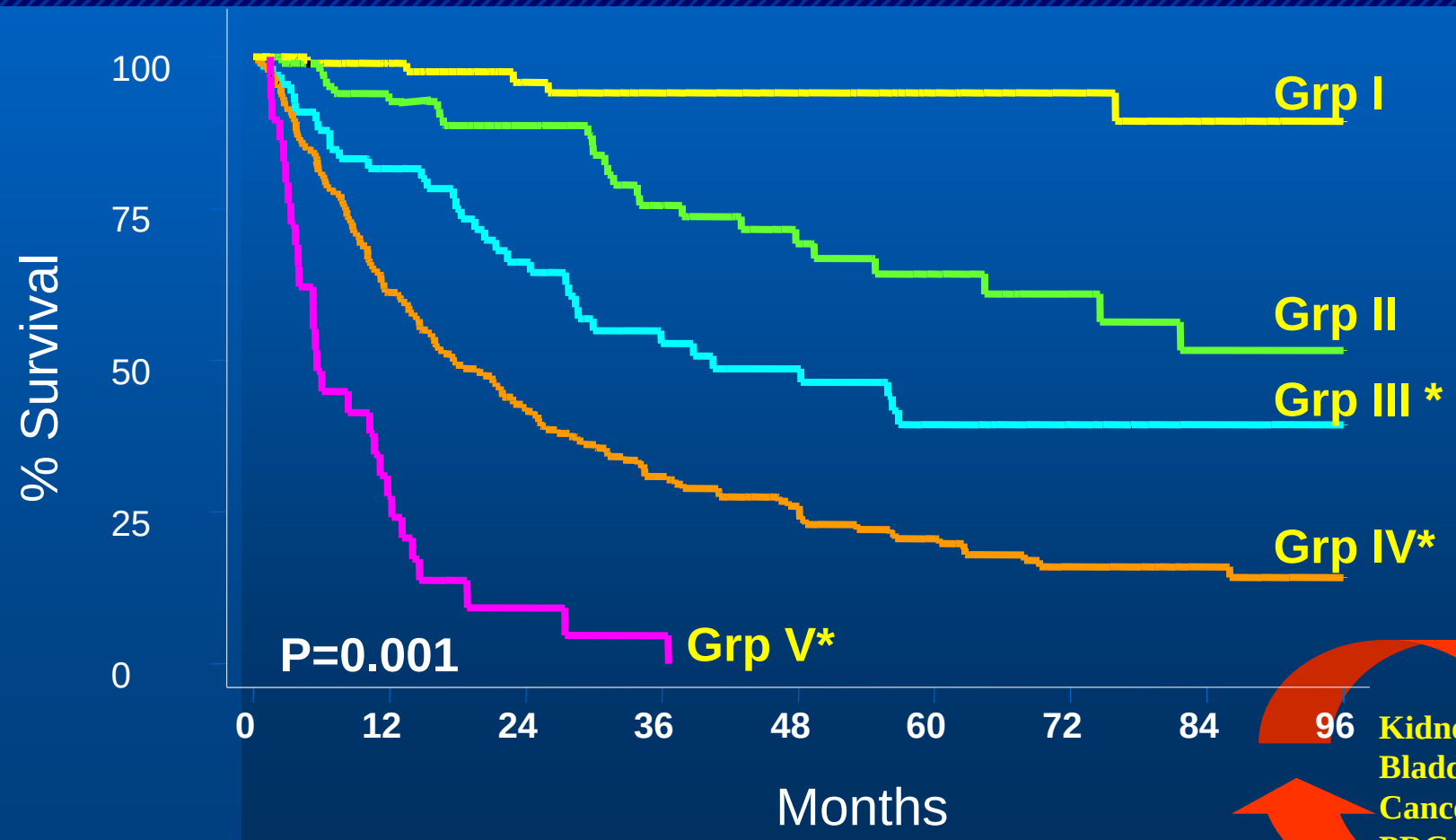
UCLA Integrated Staging System (UISS)



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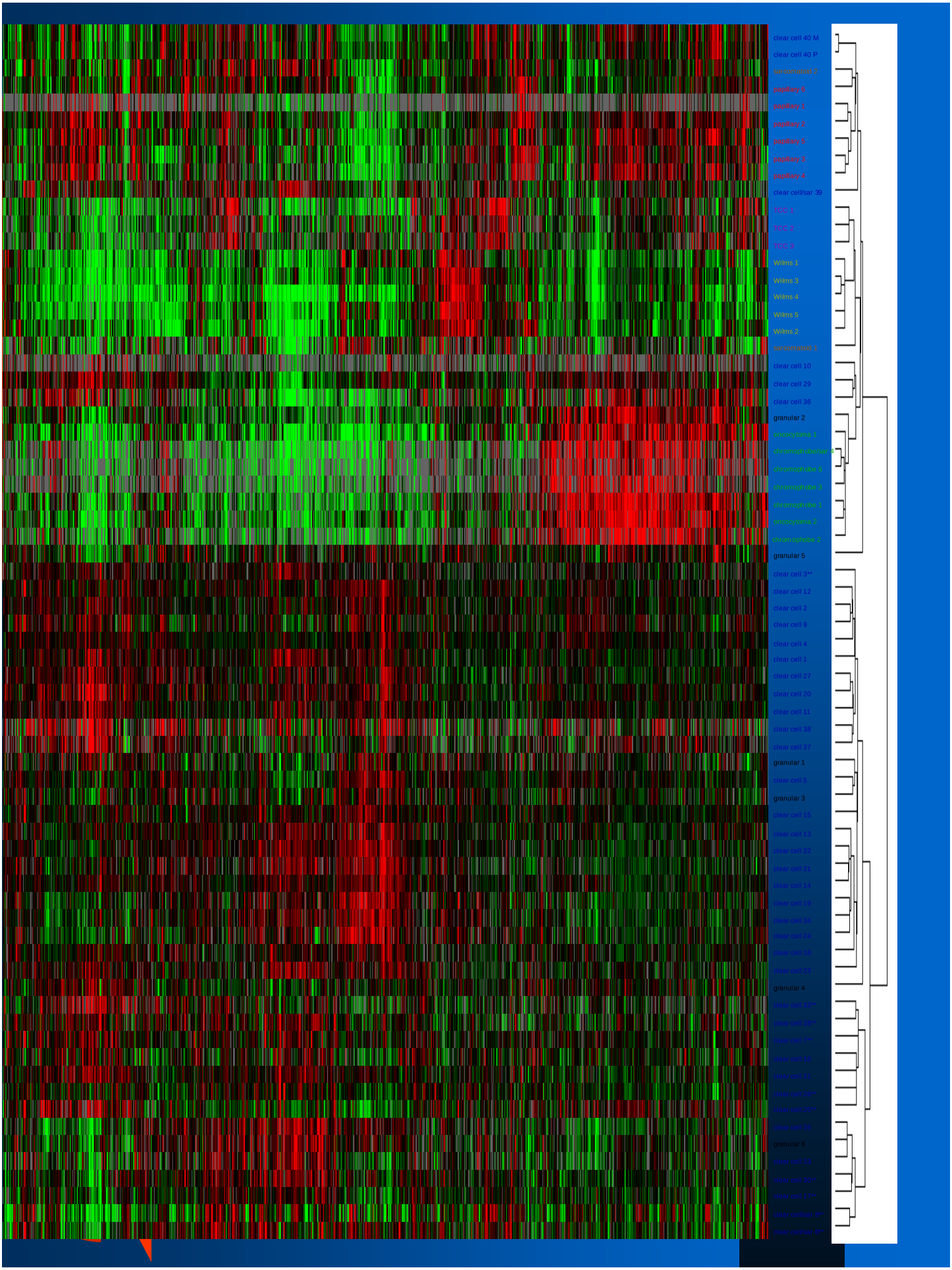
clear cell 40 M
clear cell 40 P
sarcomatoid 2
papillary 6
papillary 1
papillary 2
papillary 5
papillary 3
papillary 4
clear cell/sar 39
TCC 1
TCC 2
TCC 3
Wilms 1
Wilms 3
Wilms 4
Wilms 5
Wilms 2
sarcomatoid 1
clear cell 10
clear cell 29
clear cell 36
granular 2
oncocytoma 6
chromophobe/sar 4
chromophobe 5
chromophobe 2
chromophobe 1
oncocytoma 7
chromophobe 3
granular 5
clear cell 3**
clear cell 12
clear cell 2
clear cell 9
clear cell 4
clear cell 1
clear cell 27
clear cell 20
clear cell 11
clear cell 38
clear cell 37
granular 1
clear cell 5
granular 3
clear cell 15
clear cell 13
clear cell 22
clear cell 21
clear cell 14
clear cell 19
clear cell 34
clear cell 24
clear cell 18
clear cell 23
granular 4
clear cell 32**
clear cell 28**
clear cell **
clear cell 16
clear cell 31
clear cell 30**
clear cell 35**
clear cell 25
granular 6
clear cell 33
clear cell 30**
clear cell 17**
clear cell/sar 8**
clear cell/sar 6**

Treatment-9

- New genetic and protein signatures of kidney and bladder cancer must be correlated with known prognostic groupings

- Novel molecular biomarkers and imaging techniques would have immediate implications for treatment and later for chemoprevention trials

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Treatment-10

Develop evidence-based hypothesis-driven research efforts in palliative care for patients with advanced kidney and bladder cancers.

Treatment-10

- Sadly, over 95% 0f patients with metastatic disease die, usually with discrete metastatic patterns (brain,bone or lungs metastases from renal cancer, liver or intra-abdominal disease from bladder cancer)
- The mechanisms underlying these patterns are completely unknown
- Specific management strategies(i.e. those involving transplant, orthopedic surgery and neurosurgery) can be refined and made evidence-based

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Non-Myeloablative Allogeneic Stem Cell Transplantation in RCC

Site	No Pts	Response	GVHD	TRM
NIH	55	34%	65%	9%
Chicago	16	25%	51%	25%
MDA	14	14%	78%	36%
U Wash	6	17%	67%	17%

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Cancer Control-11

Describe the impact of kidney and bladder cancers and their treatment on the quality of life of individuals and their families throughout the cancer continuum and develop and assess interventions that will reduce morbidity and improve health-related quality-of-life outcomes.

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Cancer Control-11

- The large majority of patients with kidney and bladder cancer have early stage/easily curable disease
- The PRG estimated over 0.5M survivors in the US who must deal with sexual and urinary dysfunction, long term surveillance, second malignancy risks, all of which affect QOL

Cancer Control-11

- The field lacks investigators and instruments
- Association of smoking with both cancers and of obesity with kidney, suggests a role for behavioral interventions in both primary and secondary risk reduction

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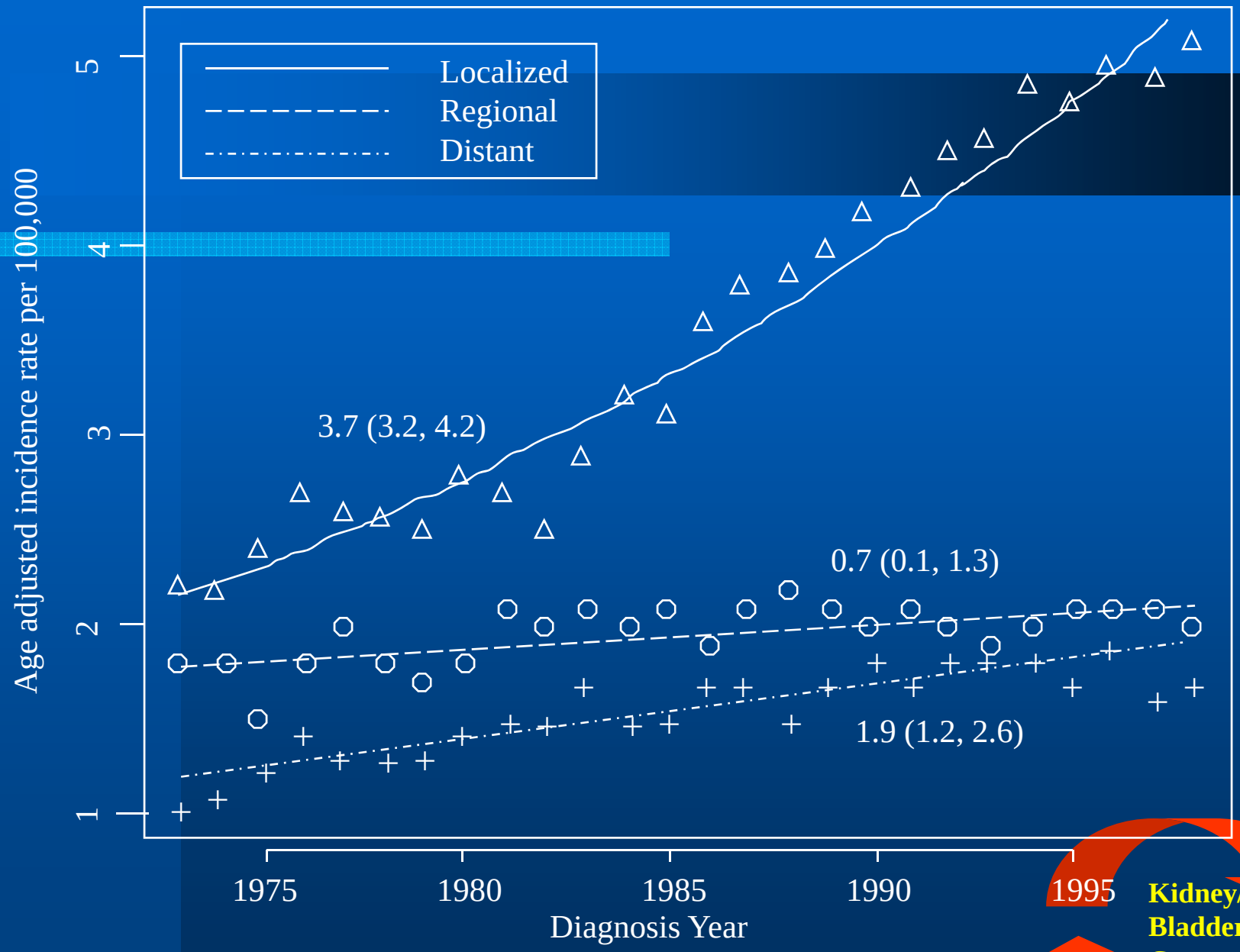
Cancer Control-12

Identify, characterize, and validate molecular markers to determine the risk of disease, enhance early detection, and predict response to chemoprevention with new chemo-preventive agents and strategies, employing new models as appropriate.



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Joinpoint regression serial error model of age adjusted incidence renal and pelvic cancers per 100,000 population by stage, as reported in SEER program during 1973 to 1998 ($p < 0.05$). Values over curves indicate annual percent change per 100,000 population. Values in parentheses indicate 95% CI.

Cancer Control-12

- Screening holds definite promise for reducing mortality from bladder cancer in high risk populations.
- VHL families, and other genetically-at-risk families, present a special opportunity to find,validate and use novel markers for RCC screening

Cancer Control-13

Identify and explore the gaps between and barriers to standards of practice and care that currently result in disparate outcomes for kidney and bladder cancer patients.

Cancer Control-13

- Women experience more delays in diagnosis, are nearly 50% more likely to die of bladder cancer, and their death rate from bladder cancer has not declined.
- Elderly patients with both cancers also seem to be under-diagnosed and treated
- African-Americans have a rapidly rising incidence and death rate from RCC

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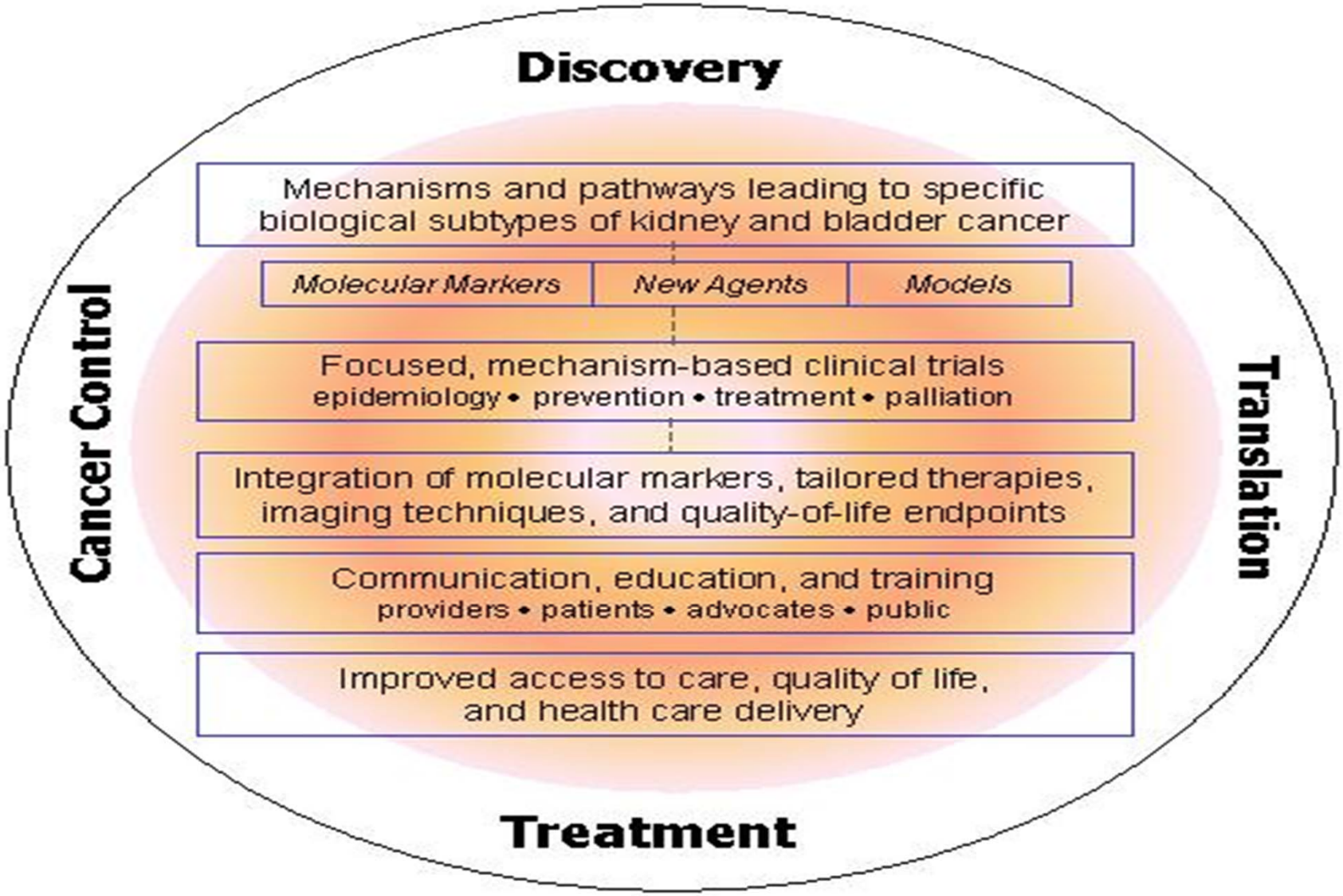
Kidney/Bladder Cancers PRG



Resources

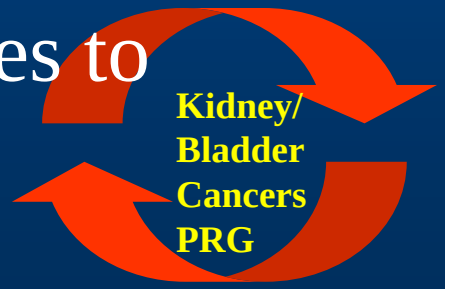
- Centers and networks of disease-specific clinical research -- [Expand definition of the Specialized Programs of Research Excellence (SPOREs) to encourage multi-institutional consortia.]

- Animal and cell-based models.

- Training

Resources

- Validated, high-quality high-throughput technologies for the analysis of DNA, RNA, and protein in tumors.
- Large, multifaceted screening and prevention studies conducted with international collaboration
- Noninvasive imaging modalities to evaluate therapeutic efficacy in vivo.



Conclusion

- Enormous opportunities exist for defining the biology of each disease which, in turn, will lead to better risk assessment, better staging, better individualized treatment and management, and improved population outcomes
- The continuum of cancer research and care encompasses all 4 areas; each must be supported for the ecosystem to thrive

Conclusion

- The lives of 24,000 Americans are taken each year by these 2 diseases

- The death rate from bladder cancer has declined. It can be reduced in kidney cancer as well

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Kidney/Bladder Cancers PRG Acknowledgements:

- PRG members (N~45)
- PRG participants (N~120)
- Jorge Gomez PRG Ex Director
- Science writers (N~13)
- Palladian Partners
- NCI OSPA: Kevin Callahan, James Corrigan, Anna Uy, Deborah Duran

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