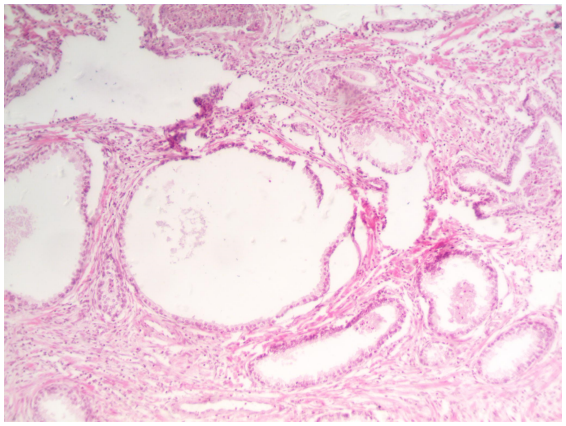

CANCER THERAPEUTIC OPTIONS

NOVEMBER 2024

ABSTRACT
We present a systems based approach to cancer therapeutics focusing on prostate cancer. We develop a method that considers the currently know steps that enables tumor cells to avoid any therapeutic. We further focus on a methodology that attempts to minimize collateral cell damage.
Terrence McGarty
TGL 211

NOTICE

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Furthermore, this document contains references to and quotes and modified charts and figures from papers and documents under the premise of “Fair Use” in order to present ideas and understandings in context. The Author has attempted to make any and all references to such material separate from those of the author per se and has referenced the source expressly in all cases. These documents are for the dissemination of ideas and have no commercial intent. Our approach herein is to take elements of what is recent in the literature focused on a specific topic and attempt to develop a tapestry image of these connectable elements. We do not necessarily provide any new or fundamental results but merely attempt to assemble elements in a systematic and holistic manner.

Communications relating to these documents and these should be sent to:
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Access to prior Technical Notes can be made via Research Gate,
https://www.researchgate.net/profile/Terrence-Mcgarty/research

Cancer Therapeutic Options[1]

Abstract

This brief note examines some key elements in dealing with the next generation of cancer therapeutics. It considers key elements which must be addressed in order to achieve a higher level of efficacy. It also points out areas of open investigation with suggestions on dealing with the complexities. The discussion focuses on personalized therapeutics rather than the broad brush approaches hitherto deployed. The discussion attempts to focus on those large percentages of patients who fail to respond to leading edge therapeutics currently in use. This Note is a speculative synthesis of known factors in prostate cancer, and cancers in general. This Note approaches the therapeutic options based upon a systems methodology utilizing established elements to create a putative whole. The conclusions, however, are speculative.

Contents

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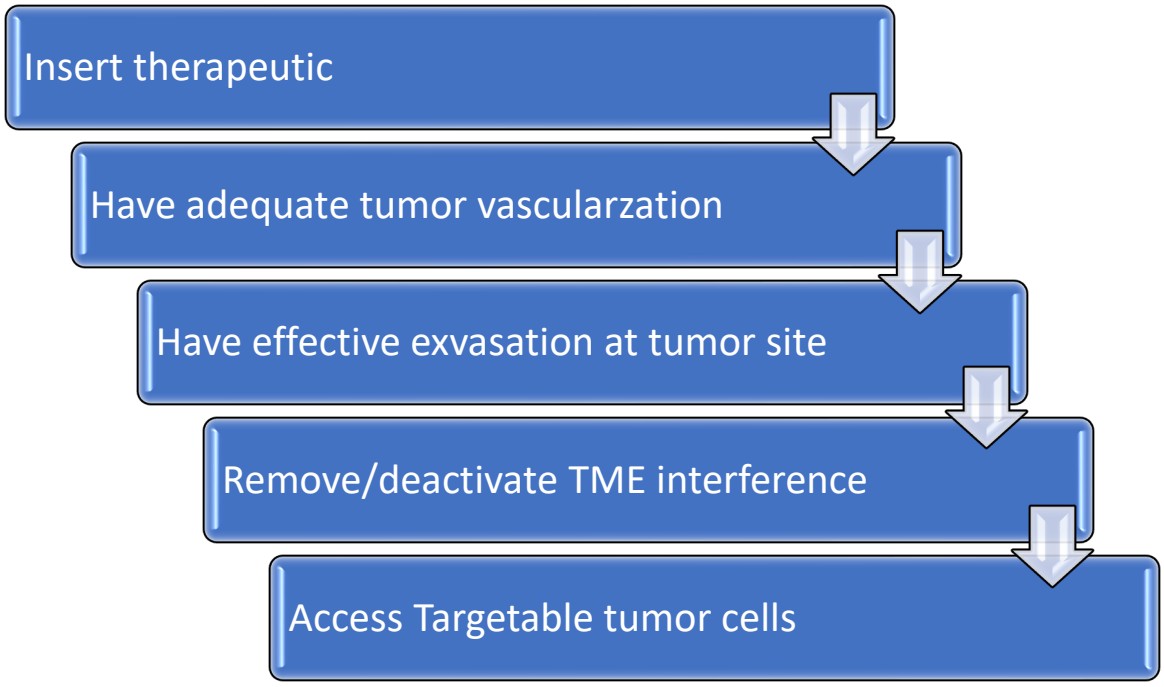
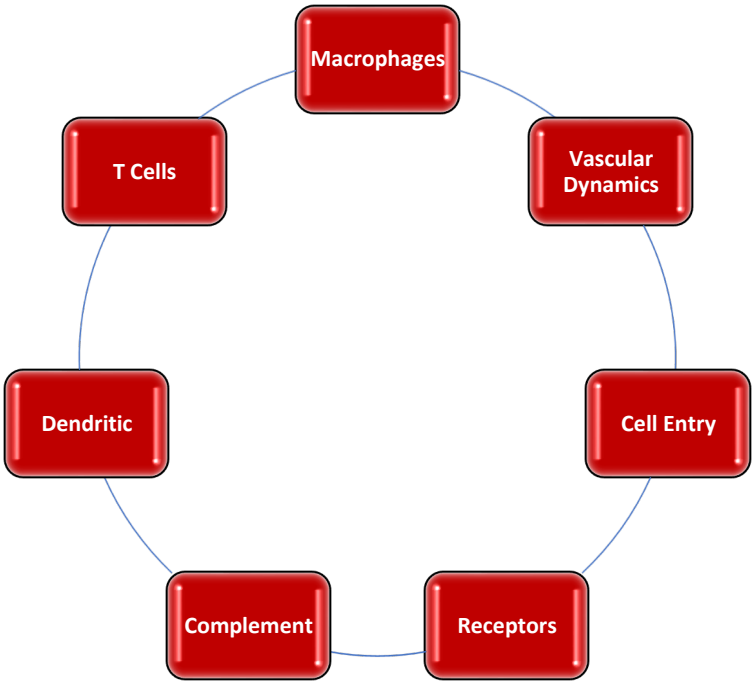
1 INTRODUCTION

We begin with a simple paradigm for a therapeutic model. The model below presents the steps which we consider. These steps are based upon current knowledge and specifically knowledge of factors which currently may inhibit effective therapeutic approaches. The approach below starts with the insertion of a therapeutic. It then contends with three barriers of entry; the vascularization of the lesion, the extravasation or outflowing of the therapeutic from the vascular system, and finally the invasion through the tumor micro environment, typically fibroblasts and macrophages. This then allows for a personalized polyspecific antibody approach, targeting personalized malignant cells. The logic is twofold. First, we know that there are many barriers to get to the malignant cells, and we try to overcome them. Second, we know that many malignancies are heterogeneous and thus demand levels of personalization. This level of personalization is attained by examining the patient's cells and using multiple surface markers to target just the malignant cells and doing no harm to other cells.



In the above there are three steps which must receive attention aside from just killing the cancer cells. Namely the vascularization, the extravasation, and the TME neutralization. These other steps are often the reason that cancer therapeutics can be ineffective in many patients. Finally we recommend personalized targeting via polyspecific antibodies. These along with drug conjugates or T/NK cell targeting may present a powerful alternative.

1. Vascularization in the tumor bed has been shown to be inhibited by the tumor stresses. This means that often the vascular structure has been compressed or otherwise compromised. This results in an inhibition of blood flow and thus makes it difficult for therapeutics to reach the tumors. There has been suggestions on a remedy of these reduced vascularization.
2. Extravasation is the process of delivering the therapeutic to the tumor from the blood stream. Typically this process may rely upon endothelial markers which attract the therapeutic to the site of the lesion. However tumor cells often have the ability to "hide" from the circulatory system.
3. The tumor micro-environment, TME, is that collection of cells and other elements that become part of the tumor site and protect and support the tumor cells. The tumor often has the ability to attract, modify, enhance and support these protective elements. Thus we must be able to break through this shell in order to deliver the therapeutic to the tumor cells.



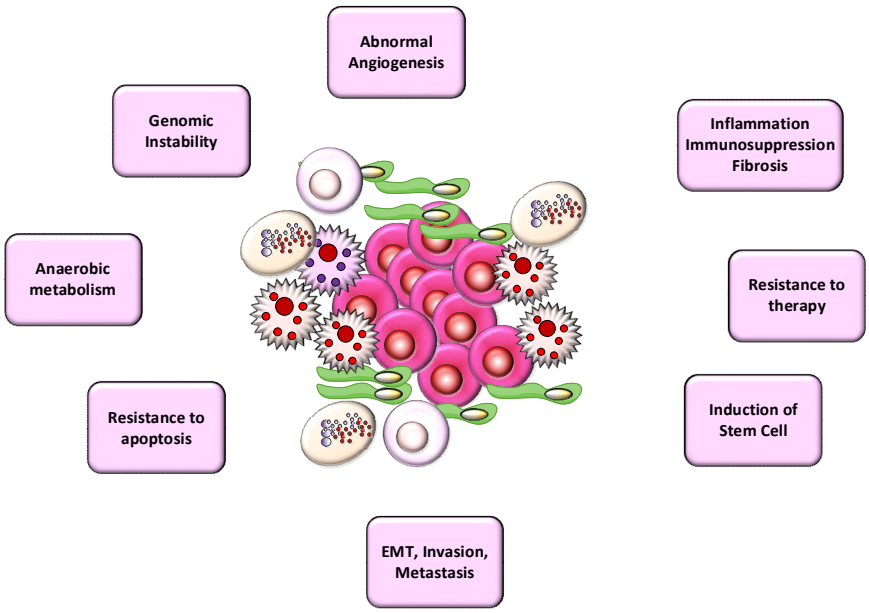
The objective the approach herein, is not to understand what the cancer cell is doing internally, but to simply develop an identify, attack and destroy process for the malignant cells, while having a high level of assurance that health bystander cells are left unharmed. In effect this is akin to some of the goals of modern warfare, strange as that may seem. One must uniquely identify the cancer cells and then one must have a personalized therapeutic that can wend its way through the mass of encumbering and protective cells to attack the specifically targeted cells.

We focus on the use of polyspecific antibodies along with drug conjugates. At the same time we may enhance this with T cell activation. The specific selection is a work in progress.

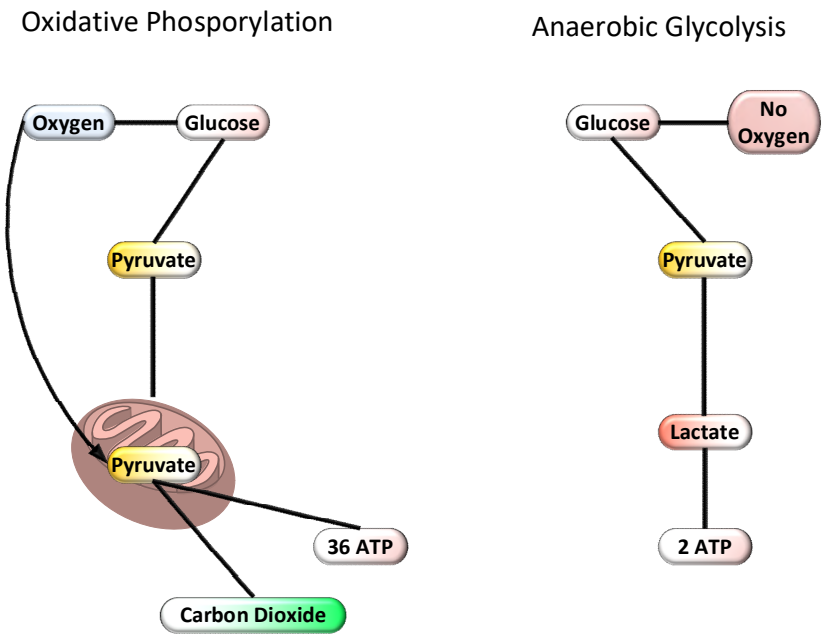
2 VASCULARIZATION

Tumors are complex in that they can be oxygen independent. The classic Warburg hypothesis does play a role, albeit modified as more becomes known. Thus as tumors progress they place pressure on the vascularization, which in turn may delimit the ability of therapeutics to reach the malignant cells. In addition, VEGF, vascular endothelial growth factor, does enhance vascular growth while at the same time the new vessels are stressed physically by the growing tumor cells.

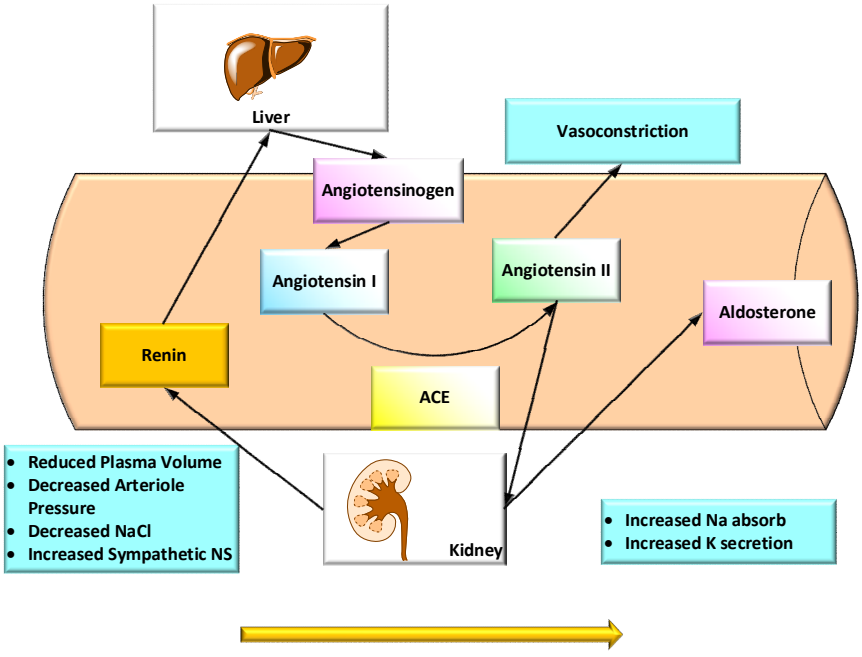
From Jain we have:



Capillary growth can cause multiple factors supporting cancer cell growth and proliferation. First is the driving of new capillaries in the tumor bed but at the same time restricting the capillary size pushing the cancer bed into a non-oxygen supported mode. The example below is the classic Warburg paradigm shown tumor growth in an anaerobic mode.

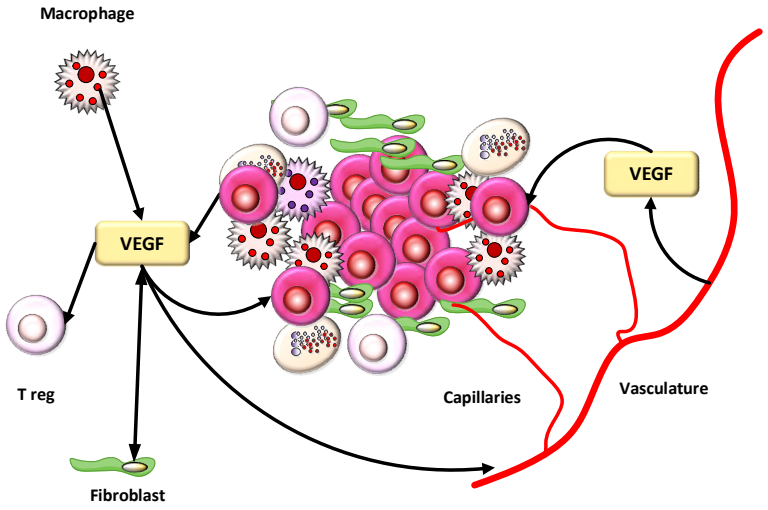


The graphic below shows the vasoconstriction resulting with ACE driving angiotensin II and ultimately also aldosterone. Thus if one wants greater vascularization, attacking the ACE or similar target allows for putatively greater and more efficient vascularity. Thus a drug like Losartan may be an effective means for increasing vascularity and allow improved tumor profusion.



Thus one possible step as has been examined by Jain et al is the use of Losartan to improve vascularity[2].

A second step is the use of VEGF controls. The graphic below shows how VEGF interacts with the tumor, the TME and the vascularization of the tumor mass. The tumor become vasculated but the tumor mechanical structure can often suppress effective vascularization. That is the reason we seek to return to improved vascularization via a multiplicity of means, thus allowing proper profusion of the tumor mass with the targeting therapeutic.



The optimal choice for effective vascularization to assist therapeutics is still a work in progress. However it is essential that the therapeutic have vascular access to the lesions.

3 EXTRAVASATION

Once in the blood stream, the therapeutic must be released at or near the lesion. Typically there are markers on the endothelium of the blood stream that facilitate this process. The specific details in cancers are not yet fully understood. In a recent paper by Tokarew et al they noted:

A recent approach to further enhance CAR T cell infiltration into solid tumours exploits the process of T cell egress: for example, by using α4 integrin mutant (S988A), protein kinase A (PKA)- mediated phosphorylation can be inhibited, stabilizing the α4 (S988A)–paxillin interaction and resulting in an increase in α4 integrin signalling. The inhibition of PKA-mediated α4 integrin phosphorylation enhances integrin αLβ2 (LFA-1)-mediated migration, a phenomenon termed integrin transregulation.

Together, increased α4 and αLβ2 integrin signalling promotes T cell extravasation from the vasculature and into the tissue, promoting T cell adhesion to the vasculature of inflamed tissue in an ICAM-1- and VCAM-1-dependent manner. In in vitro experiments, the inhibition of α4

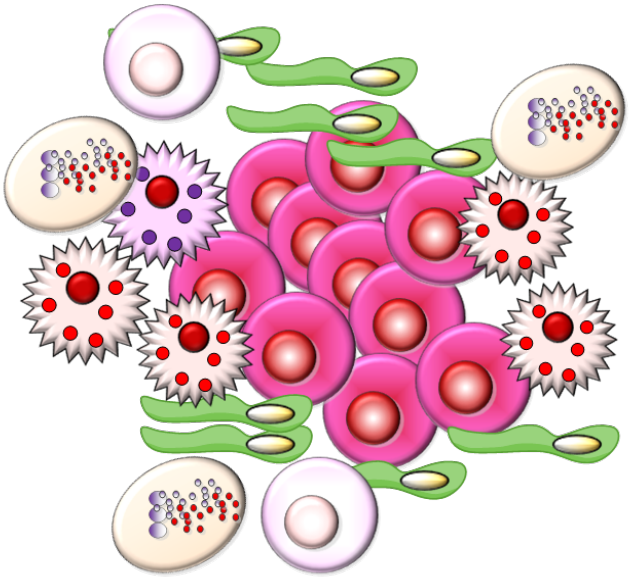
[2] The material herein references contributor to the 39th Harvard Medical School Course on Tumor Microenvironment (October 2024). See https://steelelabs.mgh.harvard.edu/tumorcourse/schedule

integrin phosphorylation promoted αLβ2- mediated T cell migration, while in vivo, the α4 (S988A) mutant mice showed a marked increase in T cell entry into ectopically transplanted melanoma tumours and reduced the growth of implanted B16 melanoma tumours.

The ICAMs can provide endothelial targeting of tumor locations. The specificity of tumor associated ICAMs is still a work in progress.

4 TME REMEDIATION

The TME is a complex of cells that surround the cancer cells and can provide protection and enable proliferation. We have discussed this generally and for fibroblasts and macrophages. We graphically show this below. This protective "shell" of cells also assist in promoting growth and spread.



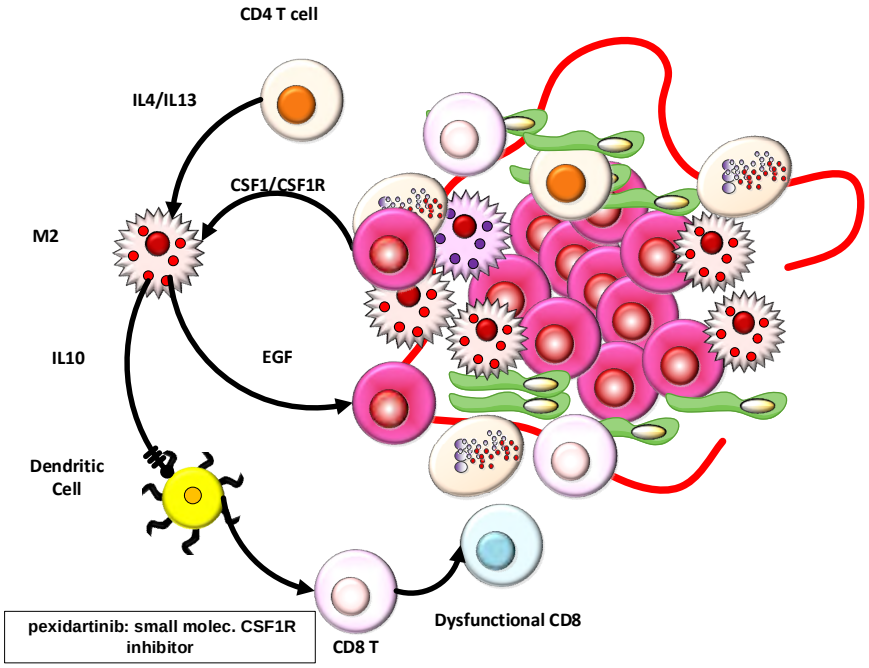
Macrophages, especially the M2 macrophages, are the primary supportive cells in the TME. As Coussens has noted[3]:

Macrophages drive poor outcome and suppress functional anti-tumor T cell response. Depletion or reprogramming MΦs will reverse MΦ/T cell ratio and improve outcome by T cell-dependent mechanisms

Coussens present the paradigm as in the following Figure. The macrophages proliferate and protect the tumor cells. We have discussed this extensively elsewhere[4].

[3] Coussens, 2024 HMS TME course, ***Identifying Immune Vulnerabilities in Solid Tumors 38th Annual Critical Issues in Tumor Microenvironment, October 2023***

[4] https://www.researchgate.net/publication/383547930_Macrophages_REDUX



Coussens remarks on Trials of this approach in M2 regulation:

Conclusion:

CSF1R inhibition/eribulin stably:

- *Reduces non-classical blood monocytes*
- *Impacts systemic immune response to favor anti-tumor features*
- *Correlates with increased peripheral Tcm and Tem presence*
- *PR/SD associated with elevated PD-1 on CD4+ T cells*

Interpretation:

- *CSF1R inhibition reprograms systemic tumor immunity and drives features of IFNg response*

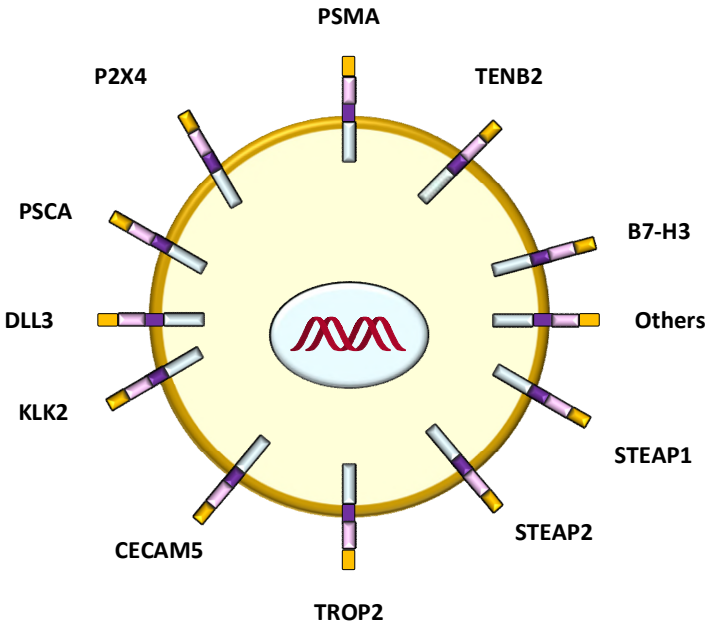
In the above, Coussens present pexidartinib as one of the therapeutics targeting the M2 cells. The following Table depicts some of the putative therapeutics that can be used to mitigate against M2 macrophages and possibly reduce the protective and proliferative elements that they present.

Therapeutic	Mode of Operation
Carlumab	CCL2/CCR2 antagonist
Duplilmuab	Il4/IL13 antagonist
Eganelisib	PI3K
Emactuzumab	CSF-1/CSF-1R antagonist
Evorpacept	CD47-SIRPa inhibitor
Leronlimab	CCL5/CCR5
Magamulizumab	CCR4 antagonist
Magrolimab	Anti-CD47
Pexidartinib:	small molecule CSF1R inhibitor
Selicrelumab	Anti cd40
Sotigalimab	Anti cd40
Trebumab	ANG2 antagonist
Umbralisib	PI3K

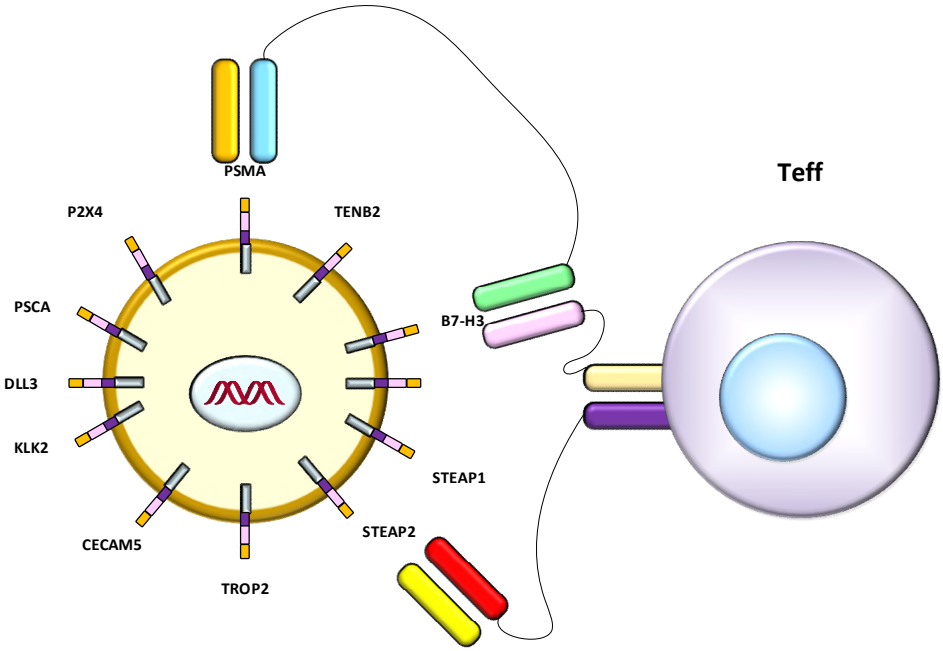
At the present time, the above have not yet been considered in an integrated therapeutic targeting of PCa.

5 TUMOR TARGETING

Tumor targeting has been evolving in various ways. The now classic approach is with HER2+ breast cancers, first using blockers like Herceptin and then by utilizing antibody drug conjugated such as TDM-1. The graphic below is one which may apply to prostate cancer. It shows 11 possible surface protein markers which may be used to uniquely identify a PCa cell.

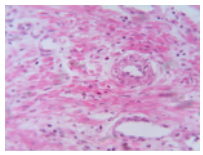


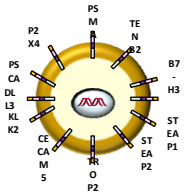
By selecting the dominant surface ligands, once can produce a personalized polyspecific antibody. This Ab may also be conjugated with a drug to kill the cell such as deruxtecan. This is a purely speculative approach, yet it may be indicative. Likewise we may attach it to a T cell as shown below to attract a personalized immune response.

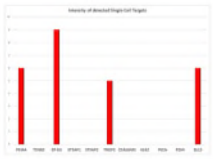


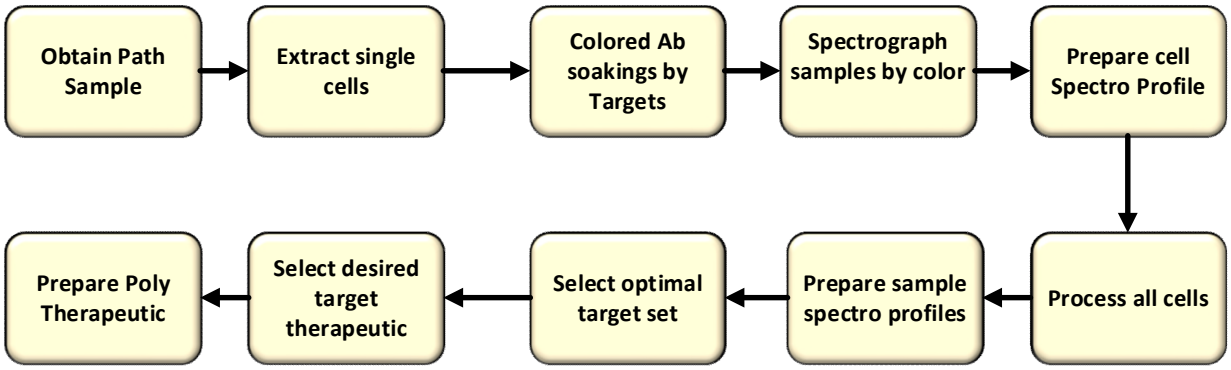
The above graphic present a 4-poly Ab with targeting of three PCa surface proteins plus attachment to T cells.

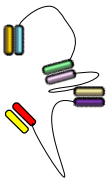
We now make a proposal as how to select targets and prepare therapeutics. The following is the process proposed:



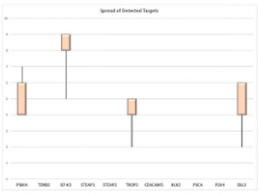








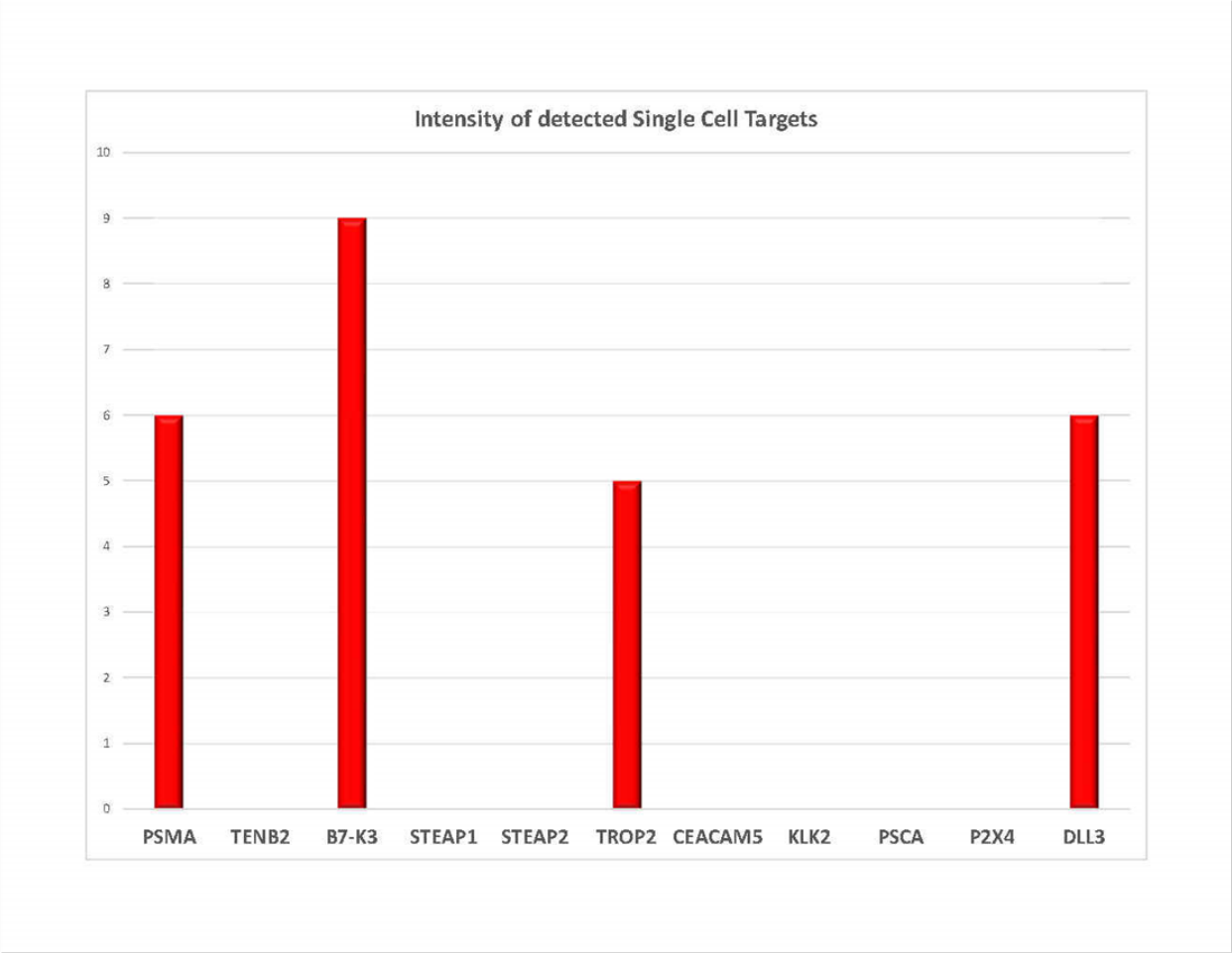
PSMA, B7-H3, DLL3



We now follow through the steps as shown above:

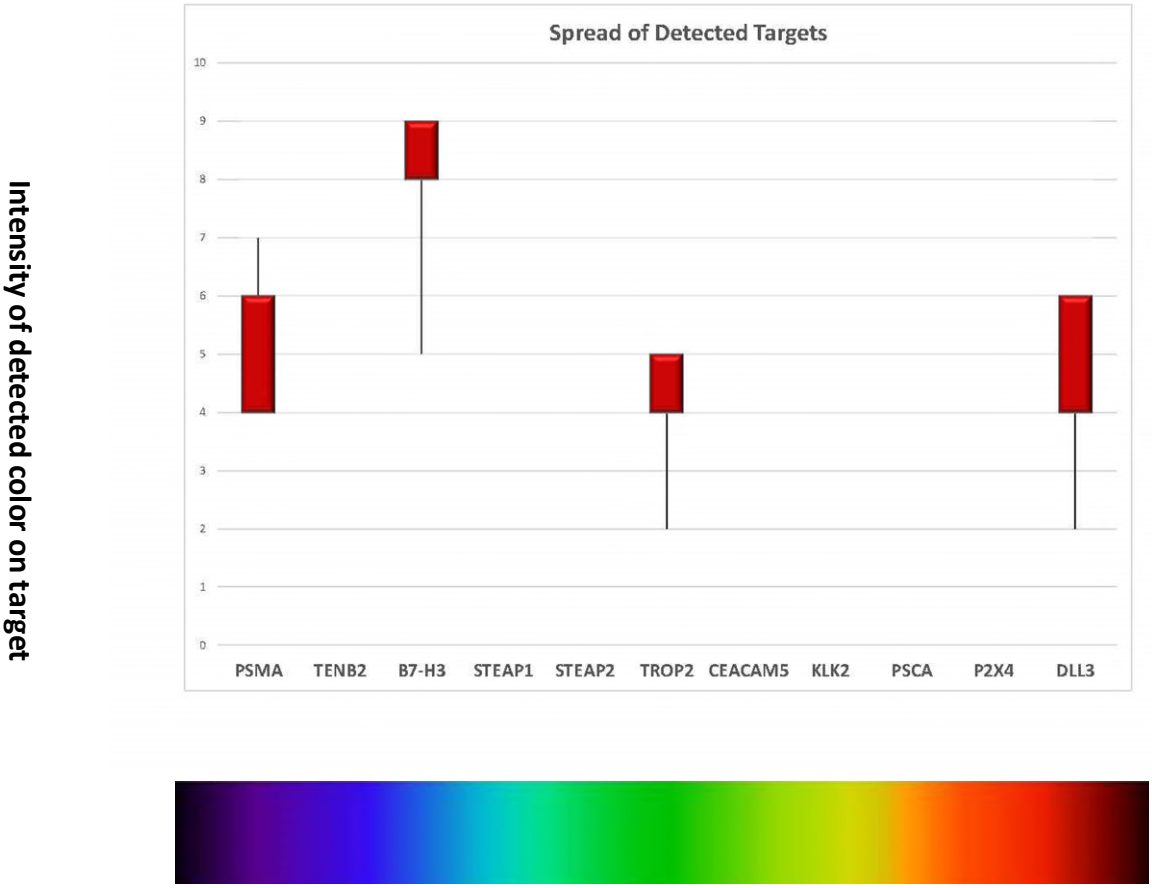
1. First obtain a pathology sample
2. The select a cell by cell from the sample. This allows a detection of the targets. Single cell sampling is essential because many cancers are heterogeneous and understanding the complexity of the lesion is essential in targeting.
3. Then using colorable Abs for each target select a specific color which can be determined by spectrographic means. Namely we target the cells with Ab that can be colored for each potential surface protein marker. This will assist in identification.
4. Scan the cell to obtain spectrographic intensity. This means we can examine each cell by a form of illuminance determining the specific protein ligands. What is important is that each cell may have ligands but the intensity of each color is a measure of the density of these ligands on the cell surface. Thus we have two metrics: presence and density. The denser the targets the better the chance for Ab targeting.
5. Prepare the cell spectrographic intensity as follows: Note that we see only 4 targets. Here we have four targets and the height is a measure of target density. The greater the density of the

spectrograph image for that color/marker the better the chance for targeting.



6. Then continue this above process for all cells examining the targets spectrographically. We thus will obtain a result for each cell. This may require a large enough number of cells to have a reliable basis.
7. Process all the cells
8. Prepare combined spectrographic data by spread analysis as shown below. This graphic is a demonstration of the spread of intensity/density of target cells and the most likely ranges of

these densities in the collection of al cells.



9. Select the optimal set of targets and then cull to a desired set. Here we show three selected targets. The methodology of optimal selection may be complex but it can often be accomplished algorithmically.
10. Prepare a polyspecific therapeutic. This may be one targeted to T or NK cells or using an Ab drug conjugates. (See Fu et al)

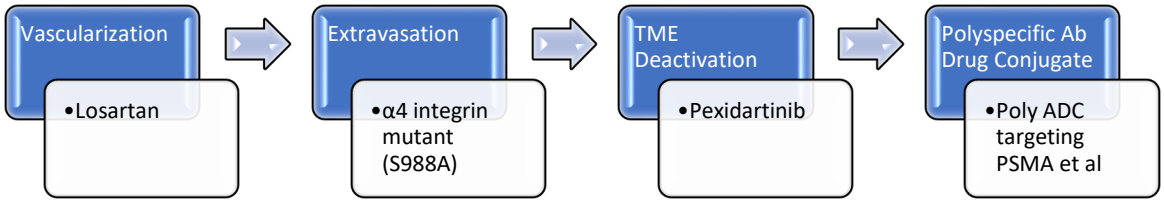
This proposal, protocol, allows individualized targeting for a specific malignancy. In fact, based upon collected clinical data these therapeutic polys can have been pre-prepared and used in a timely and cost effective manner.

Furthermore, we examine this for PCa herein but extensions to other malignancies is readily extended.

6 CONCLUSION

This Note was a speculative approach to an integrated PCa therapeutic based upon personalized targeting. The approach is suggestive of what may be an integrative methodology to deal with what is currently known as the system dynamics of PCa tumors and the barriers to targeting presented.

Thus a possible integrated therapeutic approach would be shown below:



Only the last step is personalized to a specific tumor state.

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